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IV. TWO PRE-HUNTERIAN OPERATIONS FOR ANEURYSM

(*Concluded*)

THE second operation recorded by Richard Wiseman is in the 1676 edition of his *Severall Chirurgical Treatises* and is Observation 5, page 76, of "Of An Aneurisma":—

"A man being much afflicted with a Tumour in his right Arm, occasioned by the pricking of an artery in letting bloud having tried the endeavours of several of our Profession unsuccessfully, some whereof had proposed the taking off this Arm, at the last I was sent for, and met Mr. Arris and Mr. Hollier there. Mr. Gardner was his Chirurgeon. The Tumour was large much inflamed and painfull, with little or no pulsation; but the Accident which gave rise to the Tumour enough confirmed it an Aneurisma. My opinion was, that a Tumour so inflamed was not capable of such Bandage whereby they might hope to return the bloud back into the Artery. Nor indeed was it reasonable to suppose that such a putrefactive heat as seemed to be enclosed in that Swelling was capable of being thrust back or retained long there, without making its own way by a Gangrene; and of what danger such an Eruption might be to the Patient, if a Chirurgeon were not at hand, I left to their consideration. Then in order to the removal of the Tumour there were but two ways, viz. Amputation of the Arm or cutting into the Tumour, and making Deligation of the Artery; which latter I commended to them. They assented to the Deligation; onely the Patient desired a day or two to prepare himself. We applied Empl. è bolo with a moderate Bandage to restrain the increase of the Tumour the while.

"The fourth day after we met again, and, having all things ready, the Patient was placed in a Chair towards the light. I took off the Dressings, and made a Ligature four fingers breadth above the Tumour, on which Mr. Hollier made a gripe. Some other held the Hand and lower part of the Arm, whilst I made an Incision down the length of the Tumour. That done, I threw out the grumous blood with my fingers and cleansed the wound with a sponge. Then desiring Mr. Hollier to slacken his hand, upon which the artery discovered itself by the

bloud spurting out, I passed my Needle under the upper part of the Artery and tied that, and cut off the end of the Ligature. Near the Wound made in the Artery by letting bloud there was a cartilaginous body formed, which hindred my coming to the Artery; I cut it away, then passed my Needle, and made a second Ligature. We dressed it up with Pledgits spread with the common Digestive ex terbinth. dipped in pulv. Galeni, and applied Empl. diachalcit. malaxed with ol. ros. and rowled it up to the ease of the Patient; then put him into his bed, and prescribed him an Anodyne draught to take that night. The next day I visited him, and found him in much ease: he had slept well with half the draught [which was] designed for him, and was not troubled with those fainting fits which he had been subject to before the Operation.

"The third day we took him out of his bed to dress his Arm. In taking off the Dressing we found all safe, and the Lips of the wound tending to digestion. Mr. Hollier, who held the arm above, seeing no bloud flow from the wound, for experience sake griped it harder; upon which the bloud of a sudden dropped from the fleshy parts and Capillaries in great drops, as if it had been pressed out of a Sponge. I wondered at the manner of its bleeding, not minding what he had done; but he slackning his hand, it ceased as soon. Which may show the ill consequence of over-hard binding in the dressing of Wounds, Ulcers &c. We dressed the Wound with the Digestive as before, and so continued it till the Wound was well digested. From that time we dressed it with Sarcoticks, rubbed the loose flesh with the Vitriol-stone, and hastened the cicatrizing of it with aq. medicamentos. [lime water] &c. I saw the Ligatures fall off and the Wound cicatrizing, then left it to his Chirurgeon, it being at that time indeed almost cicatrized. The patient made me a visit a while after and showed me that he could use that Arm as well as the other."

Mr. Wiseman's two assistants at the operation were noteworthy surgeons. Mr. Edward Arris, himself the son of a barber surgeon, was born in 1591 and died in 1676. He was buried in St. Sepulchre's Church, where his memorial is still to be seen. He was a man of wealth and position, living in St. Bartholomew's Hospital, a Governor, but never Surgeon, and an Alderman of Bridge Ward without. He was prolific, for his wife had twenty-three children. Liberal-minded and generous, his good qualities were not shared by his eldest son Robert, who, at any rate in his later years, proved himself to be mean and cantankerous. Excuses perhaps may be made for him because he became blind and was in such reduced circumstances that he was given a pension.

The name of Mr. Alderman Arris is perpetuated in the Arris and Gale Lectures which are still given annually at the Royal College of Surgeons of England on subjects relating to human anatomy and physiology, the lecturer being called 'Professor' and the honorarium being roughly £10 a lecture. The record of the foundation of the lectureship runs as follows, and it may be noted that the bequest was at first anonymous:—

"27th. October 1645;—This day Mr. Edward Arris acquainting this Court (of the Company of Barbers and Surgeons) that a person, a friend of his (who desired his name to be as yet concealed) through his greater desire of the increase of knowledge of Chirurgerie did by him freely offer to give unto this corporation for ever the sum of 250 *li.* to the end and upon condicion that a human body be once in every year hereafter publiquely dissected and six lectures thereupon read

. . . and if no human body may be had nor conveniently dissected in one year then the Company to distribute one half of the sum of the usual charges of a public anatomy to our own poore and the other half to the poore of St. Sepulchre's. The said worthy overture is thankfully accepted by this Court and that for the performance thereof a Rent charge of xx *li.* per annum be granted out of our lands at Holborn Bridge."

A year later: "This Court doth order that all the approved Chirurgeons according to law shall appear at all publique anatomyes for the time to come in a flatt capp, upon the penalty of 3*s.* 4*d.* and all the rest of the Livery in a Hatt." The surgeon's 'flatt capp' was green with a white ribbon round it.

Two other benefactions were made by Mr. Alderman Arris. He bought back and gave to the Company the Henry VIII's cup which is now the chief treasure of the Barbers' Company. It had been sold during the Commonwealth; and he made a skeleton of Canonbury Bess, a greatly wicked woman, who was properly hanged. Her skeleton was used for many years by the Lecturer on Anatomy—Clopton Havers amongst others—and it appears in the last plate of Hogarth's "Idle Apprentice."

Thomas Hollier, Wiseman's other assistant, was successively Surgeon for Scald Heads (1638), Surgeon (1644), and Cutter for the Stone (1663) at St. Thomas's Hospital. Mr. F. G. Parsons states that he received £36 a year as Surgeon and an additional £15 as Lithotomist. He resigned his hospital appointments in 1670 and was succeeded by his son. His house was blown up on May 26, 1676, to prevent the great Southwark fire spreading to the hospital buildings. He operated upon Mr. Samuel Pepys, the diarist, on March 26, 1658, and was Warden of the Barber Surgeons' Company when Wiseman was the Master in 1665.

It may be noted that Wiseman opened the sac of the aneurysm, turned out the clot, and ligatured the artery immediately above the sac; Hunter tied the artery at some distance from the sac, which he left untouched. The method of cure therefore, was radically different in the two methods.

THE ETIOLOGY OF THE VASCULAR SYMPTOMS OF CERVICAL RIB *

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In a small proportion of clinical cases of cervical rib the symptoms are predominantly of a vascular nature, motor and sensory symptoms being absent or very slight. Recently Telford and Stopford[1] suggested an anatomical basis to account for this predominance of vascular symptoms. In a number of dissecting-room subjects without cervical rib they examined histologically the lower trunk of the brachial plexus in the region where it lay on the upper surface of the first thoracic rib. In the eighth cadaver investigated they found in the inferior part of the lower trunk of the plexus a distinct and separate bundle of unmyelinated fibres, which they interpreted as the sympathetic fibres passing to the upper limb by way of the lower trunk and which had not yet become incorporated with and intermingled amongst the other fibres of the lower trunk; in other words, the fusion of the 'sympathetic' fibres with the lower trunk was in this instance at a more distal point than usual. In the other specimens, at the site where the lower trunk of the plexus lay on the first rib, the unmyelinated fibres were found already scattered amongst the other fibres of the trunk, although these authors noted a slight tendency for the unmyelinated fibres to reside principally in the peripheral parts of the trunk. Telford and Stopford observe that, in the special instance described, the separate bundle of unmyelinated fibres in the inferior part of the lower trunk of the plexus would evidently be more immediately exposed than the motor and sensory fibres to the risk of pressure by the subjacent rib. They further postulate that, given the same condition in the lower trunk of the plexus, the symptoms produced by a cervical rib would be predominantly vascular and would be of the nature of chronic arterial spasm induced by prolonged *irritation* of this separate exposed bundle of 'sympathetic' fibres by the pressure of the cervical rib. This prolonged spasm of the arterial stems would cause constriction or even obliteration of their vasa vasorum, with consequent nutritional changes in the arterial walls which might ultimately lead to thrombosis. That the vascular effects in these cases of cervical rib are usually confined to the arteries distal to the axillary artery is correlated by these authors with the fact that, whereas the subclavian and axillary arteries are supplied with sympathetic nerves directly from the sympathetic chain,

* Communicated to the Anatomical Society of Great Britain and Ireland, Summer Meeting, June 22, 1934.

the more distal arteries in the limb receive their sympathetic innervation from the adjacent main nerves of the limb. Of this distal nerve-supply, those nerve-fibres which issued via the lower trunk of the brachial plexus would be affected, as they lie in the form of a separate bundle in the inferior part of the lower trunk immediately related to the rib.

We had recently the exceedingly rare opportunity of examining histologically the brachial plexus from a case of cervical rib in which the vascular effects were pronounced. For the specimen and the clinical history we are indebted to Mr. Ivor Back.

CASE REPORT

(W. McKissock)

The patient, aged 37 years, a married woman without children, seven months prior to admission to hospital experienced painful tingling of the ring finger of the right hand. The nail of this digit was removed without subsequent improvement in the symptoms. During the next few weeks pain progressively spread to involve the other digits of the right hand, the hand, and finally the forearm as well, never extending above the elbow. In this period pain was felt only when use was made of the right hand or forearm, and disappeared when the limb was rested, but by the time of admission to hospital the pain had become continuous. When the hands were placed in cold water the patient observed that the right hand became white and cold, the left remaining normal. On elevation of the hands above the head, the right hand became white, but if kept hanging by the side it grew bluer in colour and felt unusually hot: the left hand did not share in any of these phenomena. For twelve months before admission the patient had a severe cough, without expectoration, and had been losing some weight.

On Admission.—The patient complained of continuous severe pain, generalized and deep-seated, in the right hand and forearm. No cutaneous anæsthesia or paræsthesia or muscular wasting could be detected, particular attention being paid to the ulnar-nerve musculature. The right arm and forearm were each $\frac{1}{4}$ in. less in circumference than those of the left side; the patient was normally right-handed, but had come to use the left more than the right owing to the pain. With the arms hanging by the side the right hand rapidly became blue and warm, whilst on elevation of the arms it at once lost its blueness and in a few seconds was white and cold. The left hand remained normal under these conditions. No accurate temperature records were taken. The right hand and forearm sweated on warming. No pulsation could be felt in the radial, ulnar, or brachial artery of the right side: pulsation in these arteries was normal on the left side. Pulsation was normal in the right axillary artery. Excessive pulsation was palpable in the right subclavian artery, so much so that (as is usual in these cases) subclavian aneurysm was suspected. On either side a cervical rib was palpable, more prominently on the right side. Radiological investigation revealed bilateral bony cervical ribs and extensive infiltration of both lungs characteristic of tuberculosis.

Operation.—In view of the severity of the pain in the limb, it was decided to operate. At operation the subclavian artery was found to be quite free from pressure by the cervical rib, even when the arm was pulled down by the side. Pulsation in it was forcible and extended beyond the cervical rib and beyond the

scalene muscles. The lower trunk of the brachial plexus lay in immediate contact with the upper aspect of the cervical rib and the first dorsal contribution to the lower trunk was stretched taut as it passed upwards and laterally to the upper surface of the cervical rib. With the exception of its extreme anterior and posterior parts, the cervical rib (which extended from the seventh cervical vertebra to the first costochrondral junction) was removed with its periosteum. The lower parts of the brachial plexus (lower trunk and first dorsal nerve) were then found to be quite free from pressure by the first thoracic rib.

At the end of the operation, faint pulsation could be detected in the radial artery. The next morning weak pulsation was palpable in the radial, ulnar, and brachial arteries. This pulsation increased slightly in intensity from day to day, but had not become normal (compared with the other side) by the eighth day, on which the patient died, the chest condition having lit up. The pain in the right upper limb, though lessened, had not been completely abolished by the operation. Complete post-mortem examination was not permitted.

HISTOLOGICAL EXAMINATION OF THE BRACHIAL PLEXUS

(D. M. BLAIR and F. DAVIES)

None of the arteries was available for examination. The specimen illustrated diagrammatically in *Fig.* 263 was removed through the site of the operation incision. It comprised the trunks, bound together in prevertebral fascia, and the distal parts of the roots of the brachial plexus. The portion of the first dorsal root included

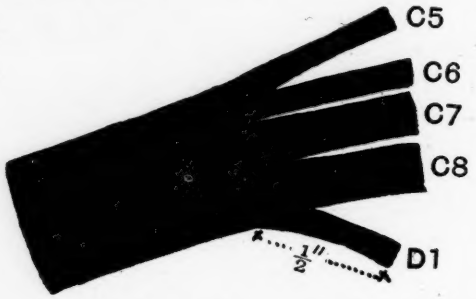

FIG. 263.—Diagram of portion of brachial plexus removed. X------X = 13·5 mm.

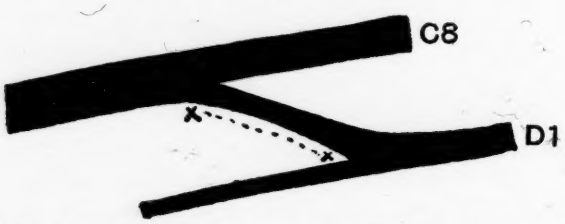

FIG. 264.—Variation in length of first dorsal nerve contribution to plexus in dissecting-room subjects. X-------X = 18 to 25 mm.

in the specimen measured 13·5 mm. In a number of dissecting-room subjects the length of the first dorsal nerve contribution to the lower trunk of the brachial plexus, from the place where it left the first intercostal nerve to the place where it joined the eighth cervical nerve, was found to range from 18 to 25 mm. (*Fig.* 264).

So at least the distal half of this portion of the first dorsal nerve was included in the specimen removed. This is of importance in relation to the fact that at no point along the first dorsal nerve or the lower trunk of the brachial plexus were we able to find an entering grey ramus.

The specimen was treated with a pyridene silver technique* which two of us (D. M. B. and F. D.) have evolved in dealing with another problem, cut serially in transverse section, and examined microscopically from end to end. In only two of the roots of the brachial plexus were grey rami seen entering—namely, one in each of the seventh and eighth cervical nerves. The other rami joining the roots of the plexus must have entered the roots proximal to the specimen. *Fig.* 265 shows the entry of a grey ramus into the seventh cervical nerve. The ramus consists almost exclusively of unmyelinated nerve-fibres which are closely packed together with very little endoneurium and very few endoneurial nuclei between the fibres. Immediately on entry the unmyelinated nerve-fibres distributed themselves amongst the other nerve-fibres in the seventh cervical nerve. The same characteristics were observed in the case of the grey ramus entering the eighth cervical nerve. Numerous unmyelinated fibres were found scattered among the myelinated fibres even in the most proximal sections of all the roots of the plexus.

FIG. 265.—Entry of grey ramus into the seventh cervical nerve. (× 60.)

Fig. 266 gives a general view of the homogeneous structure of the proximal part of the first dorsal nerve, while *Fig.* 267 is a higher-power view of a small area of the same section, near the centre, but not specially chosen. It is typically representative of the structure of the proximal part of the first dorsal nerve and shows numerous unmyelinated fibres scattered amongst the myelinated fibres, with very little endoneurium and very few endoneurial nuclei between the nerve-fibres. This is in contrast with the structure of the distal part of the first dorsal nerve, where it had come into close relation with the cervical rib. Here, as is illustrated in *Fig.* 268, the endoneurium is increased in thickness and the endoneurial nuclei are much more numerous. The nerve-fibres do not form such a compact and 'clean' picture as in the proximal part of the nerve. The lower trunk of the brachial plexus shows the same histological features, particularly in its inferior portion (*Fig.* 269), the thickened endoneurium and numerous endoneurial nuclei contrasting with the appearance of sections of the upper and middle trunks, in which the endoneurium is slight in amount and the endoneurial nuclei are few in number. The other roots of the plexus have a structure like that of the proximal part of the first dorsal nerve (with the exception of the number of unmyelinated nerve-fibres, as will be referred to below).

* This technique will be described in a forthcoming number of the *Journal of Anatomy*.

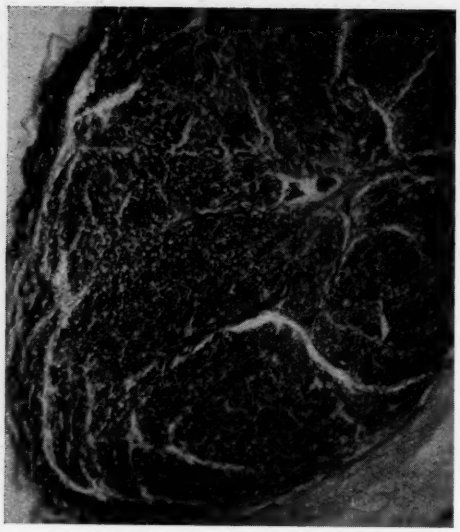

FIG. 266.—Transverse section of proximal part of first dorsal nerve. (× 37.)

FIG. 267.—Higher-power view of central part of same section as *Fig.* 266. (× 375.)

FIG. 268.—Transverse section of distal part of first dorsal nerve. (× 375.)

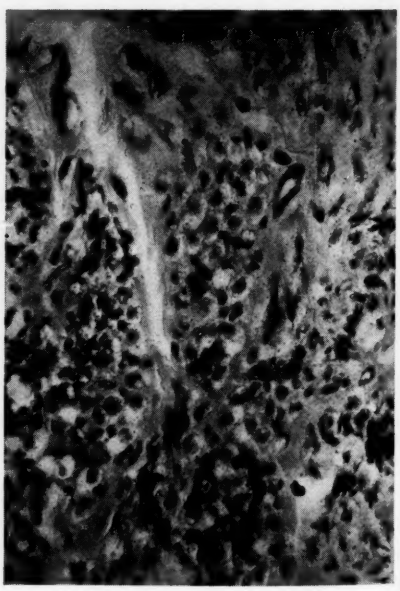

FIG. 269.—Transverse section of inferior part of lower trunk of brachial plexus. (× 375.)

Fig. 270 shows a low-power view of a section through the lower trunk of the brachial plexus. In the inferior part of the trunk is seen a distinct and separate collection of nerve-fibres which, as higher magnification (*Fig.* 271) shows more clearly, consists of a number of small bundles. This collection of nerve-fibres corresponds in position with the separate bundles illustrated by Telford and Stopford in their drawing (Fig. 413) in that it lies below the other fasciculi of the lower trunk and therefore in more immediate relation to the subjacent rib.

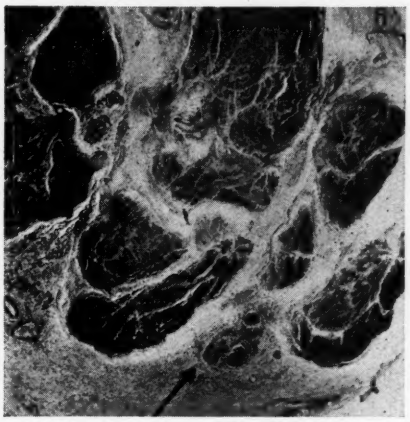

FIG. 270.—Transverse section of lower trunk of brachial plexus. Arrow points to separate collection of nerve fibres in inferior part of trunk. (× 12.)

Examination of these small bundles of nerve-fibres with a high-power objective reveals that they consist mainly of unmyelinated fibres, as shown in *Fig.* 272, which is a photomicrograph of the lower right bundle of *Fig.* 271. Although not seen in the actual small area photographed, numerous large medullated nerve-fibres are also found in these bundles. As the photograph (*Fig.* 272) shows, the unmyelinated fibres are loosely scattered in a fashion quite unlike the compact arrangement of the unmyelinated nerve-fibres in the grey rami described above. There is a large amount

FIG. 271.—Separate collection of nerve-fibres in inferior part of lower trunk. (× 60.)

FIG. 272.—High-power view of portion of separate collection of nerve-fibres in inferior part of lower trunk. (× 375.)

of endoneurium and numerous endoneurial nuclei between the unmyelinated fibres. The photomicrograph, which was taken with a panchromatic plate and the deep-red (F) Wratten filter, shows many of the nuclei as black areas owing to deep

brown-black impregnation with silver. By the use of an infra-red plate and appropriate filters[2, 3] the nuclei are rendered clearly visible and do not mask the black unmyelinated fibres (*Fig.* 273). On tracing this separate collection of nerve-fibres through the serial sections it was found to have an independent existence for only $\frac{1}{4}$ in. Both proximally and distally its nerve-fibres passed into the neighbouring fasciculi of the lower trunk and at once mingled amongst their nerve-fibres. This separate collection commenced $\frac{1}{3}$ in. distal to the junction of the eighth cervical and first dorsal nerves and, as stated above, ran distally for only $\frac{1}{4}$ in. Therefore it cannot be regarded as a grey ramus joining the lower part of the brachial plexus at a more distal point than usual. It is merely a collection of nerve-fibres (mainly unmyelinated) effecting a re-grouping within the lower trunk.

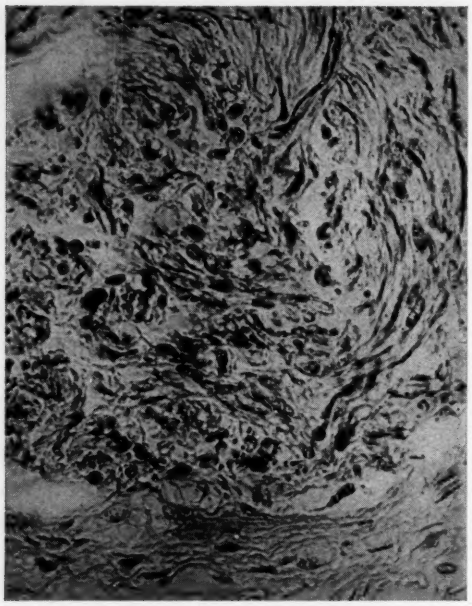

FIG. 273.—Same as *Fig.* 272. Infra-red plate. (× 375.)

Although no absolute counts were made, it was quite evident that the number of unmyelinated nerve-fibres in this separate collection formed only an infinitesimally small fraction of the total unmyelinated fibres in the lower trunk (*see Fig.* 269). In this connection it might be noted that we observed the lower trunk of the plexus to be much richer in unmyelinated fibres than the middle trunk, while the upper trunk of the plexus contained distinctly the fewest. Further, we were able to confirm the observation of Woollard[4] that the caudal roots of the plexus are richest in unmyelinated nerve-fibres. We noted no tendency for the unmyelinated fibres to reside principally in the peripheral parts of the lower trunk as Telford and Stopford described.

DISCUSSION

We agree with the view of Telford and Stopford that the clinical picture in these cases is one of *irritation* of the sympathetic (vasoconstrictor) fibres passing to the distal arteries of the upper limb, and not one of paralysis of sympathetic fibres, as other observers thought.

In the cases reported by Telford and Stopford thrombosis had taken place in the arteries of the limb distal to the axillary, and owing to the time necessary for canalization of the thrombus, several months elapsed subsequent to the removal of the cervical rib before pulsation returned in any of the large arterial stems. In the present case the rapid return of pulsation in the radial, ulnar, and brachial arteries after operation signifies that thrombosis had not supervened upon the arterial spasm. The increased tension of the arterial walls and the diminution of their lumen had alone been sufficient to render pulsation undetectable, at least by

the ordinary method of palpation. That pulsation in these arteries, however, did not immediately return to normal on removal of the cervical rib, and the incomplete disappearance of pain after this operation, suggest that the irritation of the sympathetic fibres is not due merely to mechanical pressure of the rib, but that a chronic aseptic inflammatory lesion in the nerves immediately related to the rib is produced by the pressure irritation. This lesion, of course, would only clear up gradually on removal of the exciting cause. In this connection the thickening of the endoneurium and the proliferation of endoneurial nuclei observed by us in the lower trunk of the brachial plexus (particularly in its inferior part) and in the distal part of the first dorsal nerve where it came into immediate relation with the cervical rib, appear to us to be of special significance. We interpret these histological findings as evidence of irritation by the rib in the immediately related nerves.

As stated above, the collection of nerve-fibres (largely unmyelinated) which, for a distance of $\frac{1}{4}$ in., had a separate existence in the inferior part of the lower trunk of the plexus, cannot be considered as an unjoined ramus as Telford and Stopford claim for the separate bundle of unmyelinated fibres described by them. In the present specimen the number of unmyelinated fibres in this collection forms only an extremely small fraction of the total number of unmyelinated fibres in the lower trunk of the plexus, and it is difficult to believe that irritation of these few unmyelinated fibres can be responsible for such widespread arterial spasm as seen in the case reported. Indeed, the much more numerous unmyelinated fibres in the inferior parts of the adjacent fasciculi of the lower trunk of the plexus must also be exposed to the effects of pressure by the rib, and the histological evidence supports this contention. The fact that only the lower trunk and the first dorsal nerve showed histological evidence of proliferation of endoneurium and endoneurial nuclei, and our interpretation that this lesion was responsible for the widespread irritative effects on the sympathetic vasoconstrictor fibres to the limb vessels, implies that a large proportion of the vasoconstrictor unmyelinated fibres enter the limb by way of the lower trunk, or that these fibres in the lower trunk of the plexus have a particularly widespread distribution to the arteries of the limb. We have already pointed out that unmyelinated fibres in general are more numerous in the lower trunk.

In view of the work of Ranson and Davenport,[5] supported by Donal Sheehan,[6] not all the unmyelinated fibres in the trunk must be considered to be efferent sympathetic fibres; these authors believe that many unmyelinated fibres of afferent protopathic function pass via the posterior nerve-roots to small cells in the posterior root ganglia.

As the material was not to hand for examination, we are unable to give any information as to whether the nerves on the under aspect of the subclavian artery, derived from the sympathetic chain and from the ansa subclavia (Hovelacque[7]), were in any way affected.

The lesion in the case under discussion has evidently affected principally the unmyelinated vasoconstrictor fibres in the inferior part of the plexus. It is possible that different degrees of pressure-induced chronic inflammation affect the different types of nerve-fibres in the plexus to a variable extent: hence the different clinical types of cases of cervical rib. At any rate, in our case there is no *anatomical* segregation of the unmyelinated fibres which would explain their special involvement.

If the chronic inflammatory change progresses to permanent fibrosis, this would account for the failure to relieve symptoms which is known to occur in some cases of operation for cervical rib. It therefore seems desirable that operative treatment, whether removal of the cervical rib or division of the scalenus anterior muscle allowing the rib to droop, should be undertaken as early as possible to relieve the plexus from harmful pressure.

SUMMARY AND CONCLUSIONS

1. The brachial plexus from a case of cervical rib with vascular symptoms was examined histologically in serial transverse section.

2. All grey rami joining the component roots of the lower trunk of the plexus had become uniformly distributed within the roots and trunk proximal to the region in contact with the cervical rib.

3. Marked endoneurial thickening with nuclear proliferation was seen in the first dorsal nerve and inferior part of the lower trunk of the plexus where they were related to the cervical rib.

4. It is suggested that this lesion is responsible for the irritation of the sympathetic fibres producing the widespread vasoconstriction in the limb.

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DIFFUSE INTRADUCT CARCINOMA OF THE BREAST

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Several considerations have stimulated us to report these eleven cases of diffuse intraduct carcinoma of the breast. The disease is rare—according to Cheatle and Cutler, the rarest of all forms of cancer of the breast—and yet it occurs frequently enough in any long series of cases to have a definite practical importance for the surgeon. Its clinical features differ so widely from the conception of breast cancer by which the surgeon is commonly guided that it is perfectly easy for the diagnosis to be missed, even after macroscopic examination of the amputated breast. The point we would particularly emphasize is that the breast affected with diffuse intraduct carcinoma does not contain a localized nodule of growth infiltrating the stroma, but is the site of a widespread malignant change of the epithelium of its ducts and acini affecting one-third to two-thirds of its substance. The naked-eye appearances, characteristic as they are when correlated with the microscopic picture, are so different from those of ordinary breast cancer that the pathologist who has not seen a case may easily fail to recognize that he is dealing with a malignant condition. The simulation of polycystic disease may be very close. Intraduct carcinoma is one of the conditions in which the surgeon is likely to be in doubt as to procedure, and to call for guidance from the pathologist during the course of the operation. Before it is possible to give this guidance, it may be necessary for frozen sections to be cut. The histological picture presented by the sections is most unusual. It strongly suggests that the disease starts simultaneously throughout a number of ducts and their acini, and that it does not spread from a primary focus.

So far intraduct carcinoma has most often been described in association with Paget's disease of the nipple, a condition in which it is always present in some degree. Ewing has described it apart from Paget's disease, under the term 'comedo-carcinoma'—a reference to the peculiar naked-eye appearance of the sections. Cheatle and Cutler[1] have met with 8 cases of the diffuse disease, 2 of which were in breasts also the site of Paget's disease. They consider it a highly malignant condition: 6 of their 8 patients died within four years of first coming under observation.

CLINICAL CONSIDERATIONS IN ELEVEN CASES

The average age of the 11 cases here described was 43; the oldest was 61 years and the youngest 32; 7 of the patients were married and 4 unmarried. Five had had children, and possibly a sixth in whose case the history of pregnancy is omitted from the clinical notes. The question of lactation is mentioned in 2 cases, in both of which it was abnormal. One patient was able to suckle her two children

for one month only, and the other patient, who had six children, discontinued suckling on account of pain with each of the last two babies. We have considered these particulars in some detail in order to compare them with the history of cases of Paget's disease of the nipple as we have been able to obtain this from the

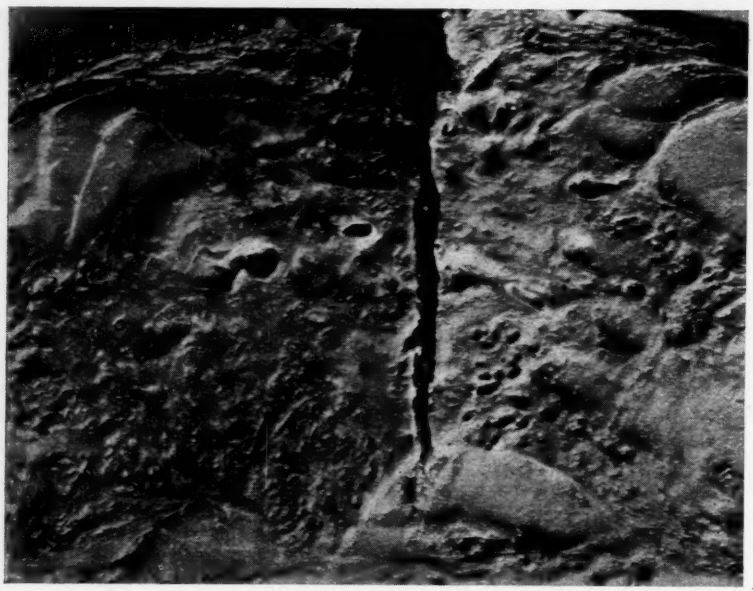

FIG. 274.—Photograph of cut surface of large breast containing diffuse intraduct carcinoma. Shows dilated ducts and affected alveoli standing out from surrounding stroma. (Unmagnified.)

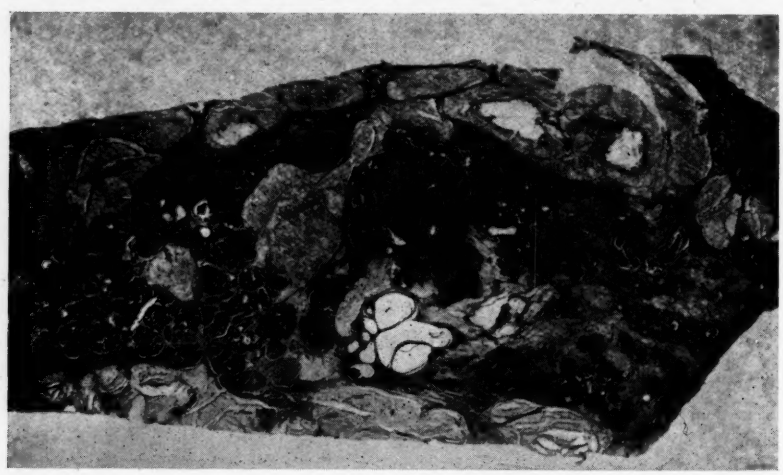

FIG. 275.—Section of same breast as *Fig.* 274 (unmagnified) showing the diffuse nature of the change.

literature. The average age of patients with Paget's disease when they first come under observation seems to be rather higher. Cheatle and Cutler reported 17 cases in which the average age was 53. A more striking contrast is found in the fact that of 37 women with Paget's disease which we have collected from the

literature, 34 were married, whereas of our 11 patients, 4 were unmarried. The two cases in our series with evidence of Paget's disease both occurred in married women.

The symptom for which these patients sought advice was either the presence of a lump in the breast or the occurrence of discharge from the nipple. The length of the history was comparatively short; in 1 case only was it over a year, and in 7 cases it was considerably less, varying from one to five months. As we have noticed in other diseases of the breast, discharge from the nipple, particularly if it is blood-stained, brings the patient to the doctor earlier than does the detection of a lump. In these cases of diffuse intraduct carcinoma, discharge was present in 7 of the 11. The discharge was blood-stained in 3 cases, serous in 3, and purulent in 1. The frequency of discharge from the nipple is particularly note-

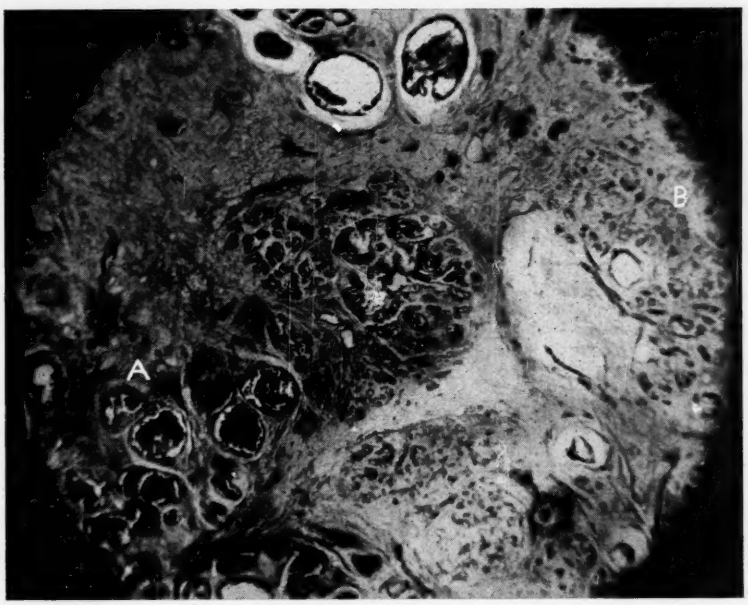

FIG. 276.—High-power view of section shown in *Fig.* 275. Unaffected breast at A, and affected alveoli at B.

worthy in view of the tendency to regard this symptom as more or less pathognomonic of simple, non-malignant duct papilloma.

Careful descriptions of the condition of the affected breasts are available in almost every case. These show that the affected breast was definitely larger than the other in 4 cases, and œdematous in 3. In 2 cases the presence of *peau d'orange* is noted; 3 of the breasts are described as 'red and shiny', and 1 of these was also said to be 'hot'. Palpation of the breast in every case except one revealed the presence of a lump, of which the patient was in some cases aware. The lump was usually quite ill-defined, and is variously described as 'indefinite', 'irregular', 'a mass of lumps', 'a diffuse hard area', 'a craggy mass'. It is frequently stated that the whole breast was œdematous, or that the breast was 'all rather hard'. Definite hard glands were present in 3 cases only. In 6 cases it is specifically stated that no glands were palpable. The nipple was retracted

in 4 cases; in 1 it was the site of Paget's disease, and this was, incidentally, the breast in which no lump was to be felt, and the case showing the least extensive growth of the series.

Personal knowledge of the last case of the series leaves us in no doubt that clinically the condition can be very puzzling. The breast was large, heavy, and œdematous; *peau d'orange* was well-marked, and over the upper inner quadrant there was a patch of bluish discoloration of the skin. An indefinite lumpiness was to be felt with no defined edge. The nipple was normal. A local excision was done, taking a wide margin of skin, and the breast sent at once to the pathological laboratory. Even after careful naked-eye examination of the cut surface the condition looked innocent, so the operation was completed without clearing the axilla. Later microscopical examination showed a most active malignant growth of the ducts, with widespread lymphatic permeation. The axillary glands were then excised and were found to be infiltrated.

MACROSCOPIC APPEARANCES (*Figs.* 274, 277)

The appearances depend on the size of the breast, and a comparison of the effect of the disease in the large fat type of breast with that in the small, rather atrophic breast largely explains the variety of the clinical descriptions. In the first place, it cannot be too well emphasized that there is no well-defined mass of carcinoma spreading into the surrounding tissue. A large breast containing much glandular tissue and a large amount of fat will be of increased consistency throughout. The cut section shows the ducts thickened and dilated, often distended with yellow secretion. The alveolar tissue looks opaque and stands out against the background of fat. The general appearances of the section reproduce the normal breast pattern, but in an exaggerated degree.

The section of a small breast with a small amount of glandular tissue and very little fat is rather different. It presents a honeycomb appearance owing to the presence of numerous small cysts formed by the dilated and distended ducts. The presence of yellow nodules of growth in some of the ducts gives an appearance to the section which should suggest duct carcinoma, and it was these nodules that gave rise to the term 'comedo-carcinoma' in Ewing's description. Certain cases of Reclus' disease present a somewhat similar picture, where the secretion in the cysts has become opaque and simulates nodules of growth. In some cases of polycystic disease it is impossible to exclude malignancy without microscopical examination, but, whereas in diffuse intraduct carcinoma there is, in our experience, always some unchanged breast tissue to be observed, in polycystic disease the change is present throughout the breast tissue. The secretion in intraduct carcinoma may be blood-stained, or there may be a golden or brown pigmentation of the connective tissue, due to absorption of hæmoglobin. This appearance has not been observed by us in simple cystic disease.

Serial sections of the breast, 2 mm. thick, may reveal small areas where the cystic formation is less marked and in which the tissue seems firmer than elsewhere. These areas, examined microscopically, show infiltration by growth of the connective tissue, but such areas are not very conspicuous, and are likely to be missed unless the breast is systematically examined. The axillary glands may be enlarged and firm and may contain obvious growth.

MICROSCOPICAL APPEARANCES (*Figs.* 276, 280–282)

The histological picture varies with the part selected for section. If the section is made of only a small part, it will show what appear to be dilated ducts

FIG. 277.—Photograph of cut surface of small breast, with diffuse intraduct carcinoma extending into the fat at the margin, M. (Slightly magnified.)

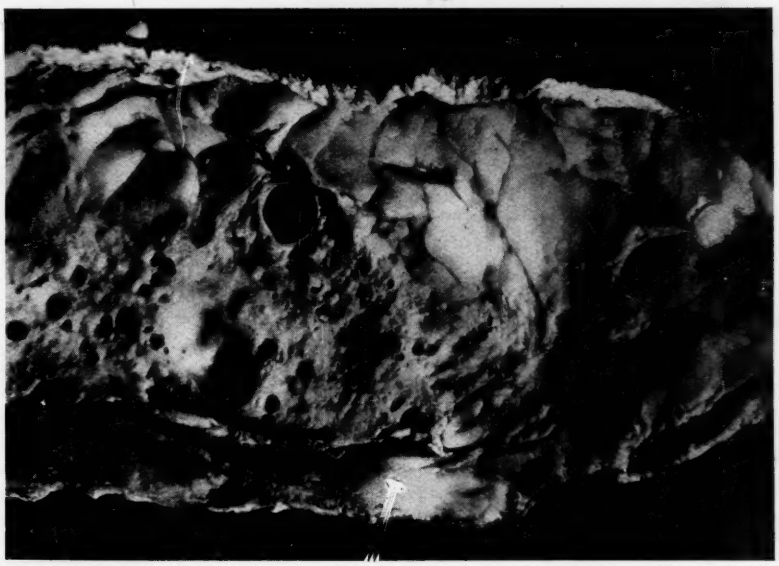

FIG. 278.—Diffuse cystic disease of the breast. Compare the similarity of the macroscopic appearance to that of *Fig.* 277. (Unmagnified photograph of section.)

containing malignant-looking epithelium, but no alveoli may be seen and no infiltration outside the duct wall. Whole section of the breast—or, where this is impracticable, of half the breast—is most helpful, both in determining the condition

of the acini and in tracing the infiltration of the stroma. Staining the elastic tissue throws light on the structure of the growth. Tubules of epithelium will be seen closely resembling the ducts with their proliferated epithelial lining, except that the elastic coat is missing (*Fig.* 282). Some of these outgrowths are alveoli, dilated

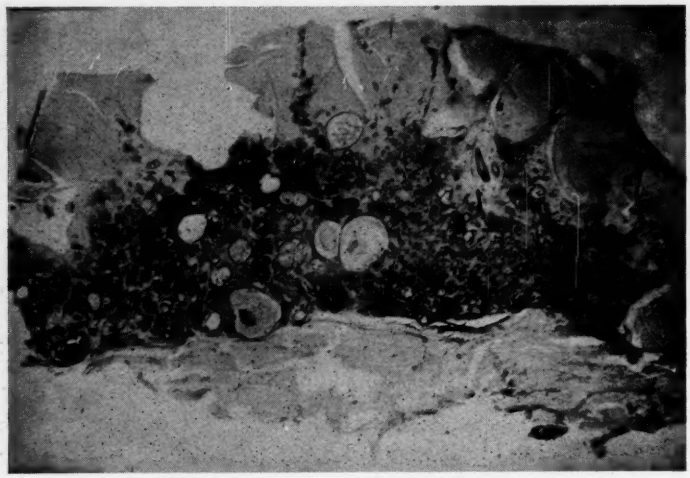

FIG. 279.—Section of same breast as *Fig.* 278. Microscopical examination showed no evidence of malignancy. (Unmagnified.)

FIG. 280.—Unmagnified photograph of stained section of breast with diffuse intraduct carcinoma, for comparison with *Fig.* 279. In this case there was widespread lymphatic permeation.

and undergoing malignant transformation. In large sections alveoli can be detected at the edge of the growth in various stages of change—an appearance that is most easily demonstrated in the larger breasts (*Fig.* 276). In other parts of the section the 'tubules' will be found to represent outgrowths of secondary infiltration of the epithelial lining of the duct. So closely do they resemble the ducts from

which they arise that at first one finds it difficult to convince oneself that their appearance is not accounted for by a fault in the staining technique. However, by careful search an outgrowth may be found actually breaking through the elastica of the parent duct (*Fig.* 282, A).

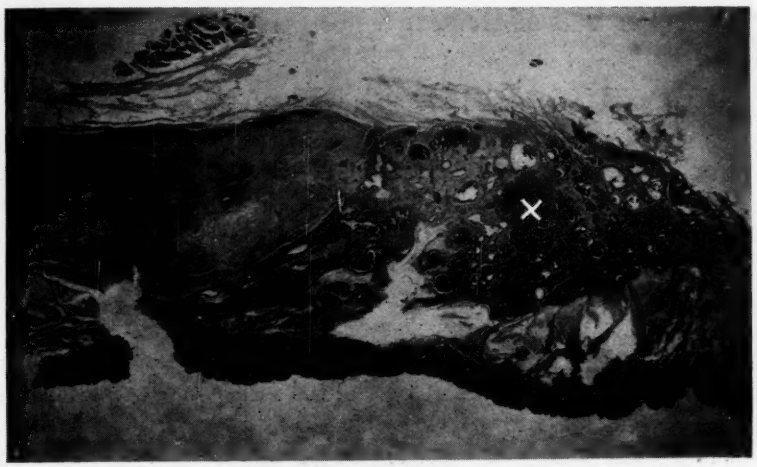

FIG. 281.—Section of small breast showing the dilated ducts containing growth and infiltration of the stroma at X. (× $\frac{3}{2}$.)

FIG. 282.—High-power view of section showing invasion of the stroma. A, Growth breaking through the elastic tissue; B, 'Tubules' of secondary growth in stroma. Inflammatory reaction well seen.

In 9 of our cases infiltration of the stroma could be detected in one or more areas. To find these areas it was sometimes necessary to make microscopic sections of the whole breast; in other cases slicing of the whole breast, followed by section of likely-looking parts, was successful. In all cases there is a more or

less well-marked inflammatory reaction in the stroma, plasma cells and lymphocytes predominating. So striking is the occurrence of the carcinomatous change in such a widespread area that the conclusion is almost irresistible that there has been a simultaneous affection of the ducts and acini throughout the greater part of the breast. From this conclusion the suggestion arises of a blood-borne stimulus, possibly of a hormonic nature.

OPERATION AND POST-OPERATIVE HISTORY

That the condition of the breast was not always recognized to be a malignant one is suggested by the fact that radical amputation was performed in only 6 cases. The remaining 5 patients were treated by local amputation of the breast and excision of the axillary lymph-glands. In one patient the dissection of the axilla was done after an interval of three months, when recurrence was obvious.

We have been able to trace the after-history of 7 of these 11 patients. Of the 6 treated by radical amputation, 2 were untraced, and 1 was lost sight of after one year. Three are living at periods of seven to eight years after operation, but one of these three shows evidence of recurrence in the chest wall and the lung.

One of the 5 cases treated by local excision of the glands and breast is alive and well twelve years after; another shows no evidence of recurrence two and a half years after operation. The most recent case was operated on nine months ago, and proved to be a very advanced case. She is so far free of recurrence.* One patient is definitely known to have died of secondary growth eighteen months after operation, and the fifth case we have been unable to trace.

RELATION OF INTRADUCT CARCINOMA TO PAGET'S DISEASE OF NIPPLE

Muir[2] has brought forward striking evidence to support the view, first advanced by Jacobaeus[3] in 1904, that the primary lesion in Paget's disease is a malignant epithelial hyperplasia within the ducts. The lesion of the nipple he believes to be due to a direct intradermal spread of carcinoma cells from the ducts, and the deep-seated infiltration in the underlying breast tissue, with which Paget's disease is so often associated, to be an outgrowth from the deeper parts of the ducts at a place where the epithelial change is more actively malignant. In 5 cases Muir was able to demonstrate an undoubted association of duct carcinoma with Paget's disease, though in 2 cases Paget's disease was discovered only on microscopic examination. Cheatle and Cutler have described 17 cases of Paget's disease all associated with intraduct carcinoma, and 6 cases of diffuse intraduct carcinoma apart from Paget's disease. Two of our cases showed evidence of Paget's disease, one on microscopic examination only.

We have sufficient evidence in the sections of our cases to convince us that infiltration of the lymphatics[4] can have no bearing on the causation of Paget's disease. The last case showed the most marked infiltration of the subdermal tissue, extending right under the skin around the nipple, but no infiltration of the epidermis itself, and no evidence of Paget's disease.

* When last seen (14 months after operation) this patient showed extensive infiltration of the skin of the chest wall.

Muir describes the epithelium confined within the ducts as being in a state of potential malignancy. The history of patients with the disease suggests that they are suffering from a much less malignant type of growth than are those with diffuse intraduct carcinoma. Our series of 11 cases seems to be intermediate between the highly malignant growths described by Cheatle and Cutler and the comparatively mildly malignant epithelial change found in Paget's disease. We conclude that in all these clinical types of growth one is dealing essentially with the same disease, which when slowly developing allows of permeation of the skin around the nipple, and when rapidly spreading leads to infiltration of the lymphatics and to widespread growth at an early stage of its history.

SUMMARY

1. Eleven cases are reported of diffuse intraduct carcinoma of the breast. The clinical history and progress of these cases are described.

2. The change is diffuse and affects both ducts and acini. It should be considered a malignant condition because infiltration of the stroma, lymphatic permeation, and outgrowth of the epithelium of the ducts can be demonstrated.

3. The widespread nature of the change and its uniformity throughout the breast suggest the action of a blood-borne stimulus, possibly of a hormonic nature.

4. This series of cases illustrates all types of intraduct carcinoma, from that of low malignancy and slow growth with which Paget's disease tends to be associated, to the highly malignant type in which lymphatic permeation is a marked feature.

The photographs illustrating the text were taken by the technician to the Pathological Department, C. Wells.

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[2] MUIR, R., *Jour. Pathol. and Bacteriol.*, 1927, xxx, 451.
[3] JACOBAEUS, H. C., *Virchow's Arch.*, 1904, clxxviii, 124.
[4] HANDLEY, W. SAMPSON, *Brit. Jour. Surg.*, 1919–20, vii, 183,

SERIAL RADIOGRAPHIC APPEARANCES OF A NEUROPATHIC SHOULDER-JOINT

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THE details and serial radiographs of the following case illustrate the different phases which were found in a neuropathic joint during its progress, and suggest that the classification of such joints into (1) hydro-arthritic, (2) atrophic, (3) hypertrophic types may merely represent these different phases of the lesion.

Mrs. W., aged 52 years, consulted Mr. Bertram Lloyd at the Queen's Hospital in August, 1931, complaining of stiffness and swelling of the left shoulder. The condition had arisen insidiously during the past few months. No history of definite trauma could be obtained. On examination the shoulder was found to be swollen and painful. The radiograph taken on Aug. 18, 1931, (*Fig.* 283) shows a marked swelling of the soft tissues around the shoulder-joint. No definite bone changes can be detected beyond a slight suspicion of increased depth of the glenoid cavity. No abnormal shadows are to be seen in the joint. The appearances are those of a hydro-arthrosis. Aspiration was performed, and following this ionization was given for three months. Slight improvement was recorded as the result, and as the condition appeared to be non-progressive, treatment was discontinued.

In March, 1933, pain caused the patient to seek further hospital treatment, and on examination it was found that the condition had progressed and the swelling had increased. The patient was admitted to the Nerve Hospital under Dr. Geoffrey Eden for investigation. A radiograph taken on March 14, 1933, *Fig*(. 284) shows : (1) that the swelling of the soft tissues had increased, (2) that the head of the humerus and the walls of the glenoid had been worn away as if the bone had been rubbed down with a file, (3) that a large collection of amorphous calcium had been stored up within the joint capsule, and (4) that the affected bones are normal in density. These appearances are typical of the so-called atrophic neuropathy.

A further examination of the patient was made on Nov. 27, 1933, when she reported that though the shoulder was troublesome she was able to perform her household duties satisfactorily. The joint area was swollen considerably and ached. The swelling and discomfort appeared to vary, being much more noticeable some days than others. No disability, discomfort, or sensory changes had been noted by the patient in any other region with the exception of the left hand, which always appeared to be cold.

On examination the uniform and regular swelling of the left shoulder-joint area was obvious. When the arm was raised above the shoulder level the movements were restricted, but there was definite abnormal forward mobility of the upper end of the humerus. The covering deltoid appeared to be hypotonic, but the area did not pit on pressure. The fullness and fluctuation of the enlarged

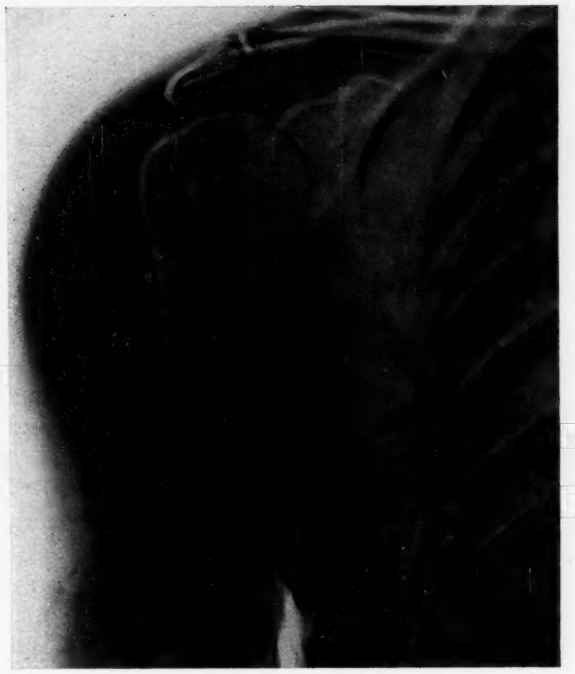

FIG. 283.—Radiograph of the left shoulder showing the swelling over the shoulder-joint and a suspicion of increase in the depth of the glenoid but no other bone abnormality. (Aug. 18, 1931.)

FIG. 284.—Radiograph showing that the upper end of the humerus and the glenoid fossa have been worn away. A large collection of amorphous calcium is shown in the joint, and there is a marked increase in the swelling of the soft tissues over the joint. It will be noted that the bone destruction is not associated with any change in the density of the affected bones. (March 14, 1933.)

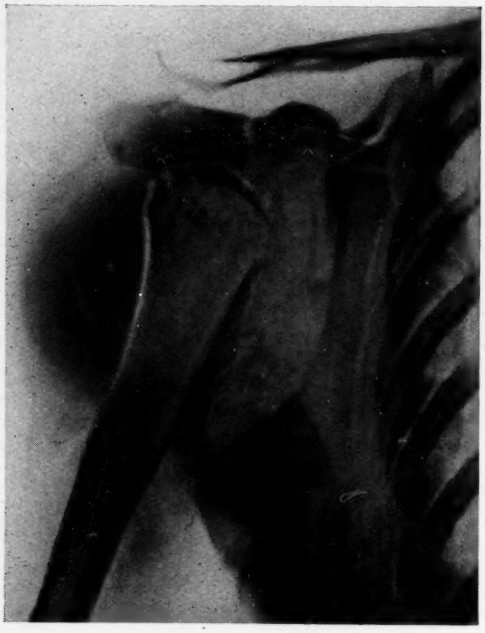

FIG. 285.—Radiograph showing a decrease in the size of the swelling over the joint, a massive bony shelf built on to the glenoid, and disappearance of the amorphous calcium from the joint capsule. (Nov. 27, 1933.)

FIG. 286.—Radiograph showing that the new glenoid shelf has undergone some absorption. (Feb. 10, 1934.)

joint could be detected in the axilla. Fluctuation could also be elicited in the region of the delto-pectoral groove. The left arm appeared to be half an inch shorter than the right. No very marked changes could be detected in the central nervous system. The pupils were unequal and slightly irregular, the reactions sluggish, but the ocular movements were full. There was anæsthesia of the posterior pharyngeal wall, absence of the palatal reflex, and a slight tremor of the tongue. No other definite abnormality could be detected. The cerebrospinal fluid showed a normal cell content, the Wassermann reaction was negative, and the biochemical tests were normal.

An X-ray taken on Nov. 27, 1933, (*Fig.* 285) showed a very marked alteration in the radiographic appearances. It will be seen that the upper end of the humerus has been worn away still more and the large deposit of amorphous calcium has disappeared from the joint cavity, but a massive bony shelf has been built on to the glenoid of the scapula, the swelling of the soft tissues not being so marked as at the previous examination. These appearances now suggest a hypertrophic arthropathy.

On Feb. 10, 1934, a further examination was made which revealed similar clinical features to those recorded at the previous examination, but the radiograph (*Fig.* 286) taken on this date showed that some absorption of the enlarged glenoid had occurred.

The destruction of bone and the storage within a joint of amorphous calcium set free in the process, and its subsequent use in the growth of bone, is a very interesting feature of the case.

The writer has previously suggested[1] that in osteochondritis deformans juvenilis coxæ (Legg-Perthes' disease) such calcium interchange may take place in the bone associated with the contents of the capsule of a joint, for in this condition we see from a study of serial radiographs that in the early phases the epiphysis takes up calcium and becomes denser, while the end of the diaphysis loses calcium and becomes radiotranslucent. Gradually the epiphysis loses its calcium, and concomitantly the end of the diaphysis approaches the density of normal bone. Eventually stability is reached when the epiphysis and diaphysis have the density and structure of normal bone.

The illustrations used in this article are reproductions made by printing through the original radiograph and a contact positive film taken from the latter. The two films, the original and its positive, are so arranged in the printing frame that the two images are not quite superimposed when the printing paper is fixed in position. The advantages of the prints obtained in this way are that the details of the dense bony structures can be preserved along with those of the outlines of the soft tissues, and a relief picture of the structures is so obtained, whereas with the ordinary straight print from a radiograph the details of the soft tissues, or of the bones, are lost because of the marked contrast in the densities.

My thanks are due to Mr. Lloyd and Dr. Eden for permission to publish this case.

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[1] BRAILSFORD, JAMES F., *The Radiology of Bones and Joints.* London: J. & A. Churchill.

RENAL-ADRENAL ADHERENCE

By T. B. DAVIE

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DEVELOPMENTAL and other non-pathological abnormalities of organs at times assume considerable clinical importance, particularly to the surgeon. Variations of this nature in the adrenals are not often met with, and as the total number of operative procedures concerned with these glands is very small, there is little call for the surgeon to take note of minor variations in their size, shape, position, or vascular supply. Furthermore, the great majority of operations on the adrenals aim either at complete excision of the organ or, more rarely, at the removal from it of tumours such as the rare phæochromocytoma, or chromaffinoma. In view, however, of the vital importance of these organs it is obviously a matter of the greatest concern that in the numerous operations nowadays performed upon the kidneys every possible precaution should be taken to prevent serious damage to the adrenals. A perusal of the text-books of surgery in general use will reveal that, whereas great stress is always laid upon the determination of the existence of a functioning kidney on the unaffected side prior to the undertaking of a nephrectomy, the question of the possible interference with the function of the adrenals by such operative procedures receives little or no attention. This is in all probability due to one or other of three reasons: (1) In the great majority of cases nephrectomy is effected without any damage to the adjacent adrenal capsule; (2) No recognized pre-operative method exists for determining the presence of adrenal abnormalities; (3) The existence of a not uncommon abnormality in the renal-adrenal relationship which renders serious damage to the adrenal inevitable in the course of a nephrectomy is not sufficiently appreciated.

In the course of the routine performance of approximately 1500 post-mortem examinations I have on 6 occasions met with a degree of bilateral renal–adrenal adherence which would have rendered impossible the removal of the kidney without the coincident removal, or serious laceration, of the adrenal gland. The accompanying photographs (*Figs.* 287, 288) show this condition in the case of a young woman of 22 years. In all these cases the small amount of loose connective and fatty tissue which usually separates the antero-superior surface of the kidney from the postero-inferior aspect of the superposed adrenal gland was absent in whole or part; and in no case could a nephrectomy have been performed without coincident adrenalectomy. In some of the cases the lower portion of the adrenal was thinned out and applied closely to the upper third of the anterior surface of the kidney, and section showed either complete absence of any capsular connective tissue between the two organs, or else the presence of only a single attenuated layer of fibrous tissue separating the two organs and serving as a capsule for both. The accompanying microphotographs illustrate the two degrees of adherence referred to (*Figs.* 289, 290).

In some of the cases the renal capsule appears to be continuous with that of

the adrenal, i.e., the two organs appear to be enclosed in a single fibrous-tissue capsule. This is always more marked on the anterior aspect, and usually the continuity of capsule is localized to the central portion of the inferior border of the adrenal gland. Even in the most pronounced of these cases there is always a small interspace filled with connective tissue between the infero-mesial angle of the adrenal and the kidney. In the cases where the degree of adherence is less marked, the separate capsules of the two organs are fused over the greater part of their surfaces of contact, even though the whole of the inferior border of the adrenal appears to be free and capable of being raised slightly from the underlying kidney.

The cause of this condition is readily appreciated from a study of the development of the adrenals. The adrenal cortex is developed from the mesial aspect of the upper, or cephalad, end of the Wolffian ridge, from the lower end of which

FIG. 287.—Renal-adrenal adherence. Right kidney showing marked adherence along the middle portion of the inferior border of the adrenal.

FIG. 288.—Renal-adrenal adherence. Left kidney. The incision shown about one-third up from the inferior border of the adrenal was made for the purpose of microscopical section.

is developed the testis or ovary; while the kidney lobules are developed from a mass of undifferentiated cells lying some distance below this. When, about the second month of intra-uterine life, the gonads migrate downwards, the adrenal cortex approximates itself to the kidney. At this stage the fœtal adrenal cortex is considerably larger than the kidney and it envelops the upper pole of the collection of renal lobules. Normally the further development of these two structures proceeds independently, each becoming enclosed in its own distinct fibrous tissue capsule with the intervention of a small amount of fibro-fatty tissue. It can, however, readily be appreciated that the close approximation of the two organs in the second and third months of intra-uterine development may at times result in a more intimate relationship, which may persist into adult life. On this hypothesis is based the explanation of the presence of adrenal 'rests' in the kidney, and the acknowledged presence of these provided the anatomical basis for Grawitz's

FIG. 289.—Renal-adrenal adherence. Section showing complete absence of capsule or inter-glandular tissue. (× 50.)

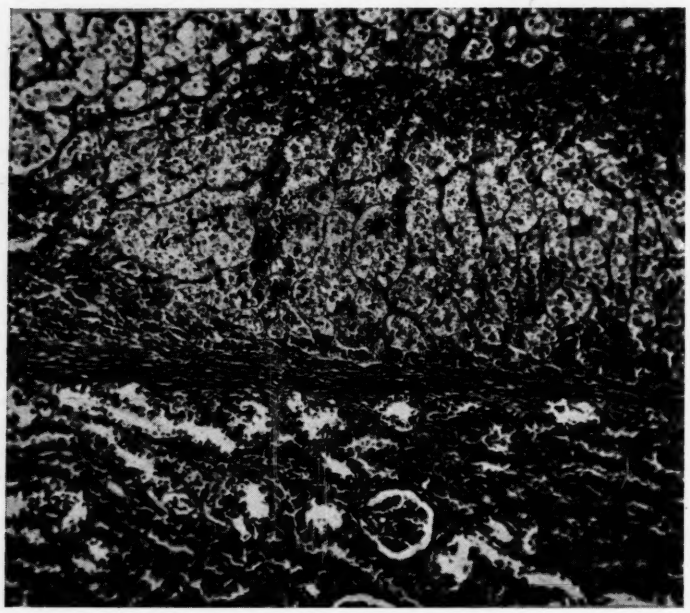

FIG. 290.—Renal-adrenal adherence. Section showing single thin fibrous capsule serving for both organs. (× 80.)

theory of the origin of the hypernephromata. These 'rests' are usually of small size and are found in various situations within the kidney, though mainly subcapsularly or interlobularly in the upper pole. That the persistence into adult life of the fœtal condition of intimate relationship may be on a much larger scale, though more superficial, is well illustrated in the cases under discussion.

A careful examination was made in all these cases for evidences of other forms of developmental abnormalities, with completely negative results. In particular, in none were there macroscopic evidences of 'adrenal rests' within the renal parenchyma, nor were any of these 'rests' discovered in the considerable number of sections cut for microscopical examination. As all the 6 cases referred to were adults, it is not surprising that in none of these were found any ectopic adrenal fragments, but in view of the frequent occurrence of such scattered nodules of adrenal cortical tissue—especially on and near the liver and in the pelvis or along the round ligament or spermatic cord—in children, it would be of interest to know whether adrenal nodules of this type are more frequent in children with renal–adrenal adhesions than in those in whom the normal relationship exists between the kidney and the adrenal gland.

As stated above, there is at present no way of foretelling the existence of this condition, and it follows that nephrectomy in these cases inevitably leaves the patient with only one intact adrenal gland. The unintentional removal or laceration of an adrenal gland under these circumstances will probably result in considerable hæmorrhage, and thus add to the dangers of the operation. The intimate connection of the adrenal medulla with the solar and cœliac plexuses of sympathetic ganglia and nerves must surely imply a severe degree of shock when these nervous connections are rudely severed, and it is just possible that some of the otherwise inexplicable early deaths following nephrectomy by competent surgeons may be the result of this. The condition of renal–adrenal adherence is apparently always bilateral, and any subsequent operation on the remaining kidney is thus fraught with the gravest of dangers. Fortunately the surgeon will but rarely be faced with this danger, but there is one condition in which it should be borne in mind—namely, in nephrolithotomy performed on a single remaining kidney. The usual operation for renal calculus, including, as it does, the delivery of the kidney on to the surface through a lumbar incision, would, in the presence of renal–adrenal adherence, result in laceration of the single remaining adrenal with serious or fatal result. Such a result could be obviated only by avoiding the manœuvre of delivering the kidney from its bed; and whereas it is obviously incumbent upon the surgeon to take this special precaution in cases of nephrolithotomy in which it is *known* that earlier nephrectomy resulted in coincident adrenalectomy, it is a matter for serious consideration whether this should not be recommended as the procedure to be adopted in *all* cases of nephrolithotomy performed on patients possessing only one kidney. In the absence of definite knowledge of the condition of the adrenal on the side of the old nephrectomy it can hardly be regarded as justifiable to presume that it is intact, particularly in view of the fact that the lumbar route of approach to the kidney exposes first the posterior surface and lateral border of the kidney, from which nothing at all can be learned as to the possibility of the existence of an adherent adrenal gland. Only when the kidney has been withdrawn from the depths of the wound to or near the surface does such a condition become apparent, by which time severe damage may have been done.

In discussing this matter with the surgeons of the hospitals from which the post-mortem experience was gained, the impression was gathered that when in the past portions of adrenal tissue were occasionally found attached to kidneys removed surgically, the operations performed had been regarded as suspect—that is to say, the surgeons felt that probably they had been a bit careless in the freeing of the kidney from its bed. One of these surgeons has recently made a careful examination of the kidneys surgically removed and has twice met with the condition of renal–adrenal adherence. In one case the complete adrenal gland was removed intact with the kidney, in the other case a large portion of the gland was found adherent to the kidney. These facts have been emphasized in the hospital case sheets of the patients, who have been instructed that owing to an abnormal arrangement of their organs it is most important that their hospital case sheets should be consulted before any further operation is performed upon their single remaining kidney. That such subsequent operations are occasionally necessary must have been the experience of most surgeons working in the field of urology, and even though, by the law of chance, the possible occasions on which the condition of renal–adrenal adherence will complicate operations of this type is very small, the issues at stake are too high to justify neglect of the precautions by which an almost inevitably fatal accident might arise.

I have much pleasure in acknowledging my indebtedness to Dr. H. H. MacWilliam and Mr. Kirk Wilson of Walton Hospital for permission to make use of the material on which this communication is based, and to Mr. Wilson for his co-operation in the matter of the search for evidence of damage to the adrenals in all cases of nephrectomy at the hospital.

COLLECTIVE INQUIRY BY THE FELLOWS OF THE ASSOCIATION OF SURGEONS INTO GASTROJEJUNAL ULCERATION

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TWENTY-FIVE years ago in his classic paper, "Jejunal and Gastrojejunal Ulceration following Gastrojejunostomy", Paterson[1] said that the fear of the occurrence of this condition cast a faint shadow over the otherwise admirable results of the operation, and he expressed the opinion that the incidence was under 2 per cent and that there were signs that this was diminishing. With the passing years the shadow has grown more dense. Increasing recognition of the symptoms, and perhaps a keener and more persistent investigation of unsatisfactory results, have resulted in a gradual rise in the estimated risk of post-operative ulcer.

Paterson distinguished two kinds of these ulcers: (1) Jejunal—situated in the jejunum; and (2) Gastrojejunal—situated on the anastomosis and extending to the gastric or jejunal mucosa, or both. The latter term has been extended by the profession at large to include all forms of post-operative ulcer. I would suggest that in order to avoid confusion the term 'secondary peptic ulcer' be used as a general term which would cover all varieties of post-operative ulcer. Individual ulcers should be called 'jejunal', 'anastomotic', or 'gastric', according to their exact situation. Some, indeed, may be duodenal, as after gastroduodenostomy.

INCIDENCE OF SECONDARY ULCERATION

Very wide estimates of the incidence of this condition have been made, from under 2 per cent by Paterson to over 20 per cent from one New York clinic. One reason for this difference is lack of uniformity in the method of arriving at the estimate. It is obviously misleading to make it from an analysis of all cases of gastrojunostomy, irrespective of the lesion for which the operation was done. It is generally agreed that gastro-enterostomy for duodenal ulcer is the operation most likely to be followed by secondary ulceration.

In the Collective Inquiry by the Fellows of the Association of Surgeons of Great Britain and Ireland the various operations have been analysed in relation to the three main gastric lesions, viz., duodenal ulcer, gastric ulcer, and carcinoma. In this way it is possible to arrive at some reasonable estimate of the risks in various operations for different lesions. These have been analysed in *Table I*, and it is important to note that the cases here considered are not necessarily the same as those in the analysis of individual ulcers. *Table I* covers a period of operations done in the five years ending 1930, while the individual cases of ulcer were collected over a period of ten years, 1923–32 inclusive. This accounts for certain minor differences between the two.

Table I.—INCIDENCE OF GASTROJEJUNAL ULCERATION FOLLOWING VARIOUS OPERATIONS

	Males	Females	Traced	Gastrojejunal Ulceration		Percentage of Combined Proved and Suspected Cases
				Proved by Operation	Diagnosed by Symptoms	
Gastrojejunostomy*						
1. Posterior Gastrojejunostomy:						
For duodenal ulcer ..	2310	424	1730	70 (4·04%)	77	8·49
For gastric ulcer	670	214	507	27 (5·32%)	26	10·45
For gastric carcinoma ..	151	69	140	0	0	–
With excision of gastric ulcer	84	28	105	0	0	–
With excision of duodenal ulcer	2	0	2	0	0	–
With excision of gastric ulcer and duodenal ulcer ..	1	1	1	0	0	–
With cautery of gastric ulcer	19	5	24	0	0	–
2. Posterior Gastrojejunostomy with Entero-anastomosis:						
For duodenal ulcer ..	48	9	33	1 (3·3%)	1	6·6
For gastric ulcer	29	20	28	0	0	–
For gastric carcinoma ..	8	6	5	0	0	–
3. Anterior Gastrojejunostomy:						
For duodenal ulcer ..	103	13	85	6 (7·06%)	2	9·4
For gastric ulcer	74	41	85	1 (1·2%)	0	–
For gastric carcinoma ..	49	25	47	0	0	–
With excision of gastric ulcer	1	2	3	0	0	–
With cautery of gastric ulcer	3	0	3	0	0	–
4. Anterior Gastrojejunostomy with Entero-anastomosis:						
For duodenal ulcer ..	42	4	25	6 (24·0%)	1	28·0
For gastric ulcer	21	7	23	1 (4·34%)	0	–
For gastric carcinoma ..	32	12	31	0	0	–
5. Pyloroduodenostomy:	1	1	1	0	0	–
Gastroduodenostomy for duodenal ulcer	34	5	29	1 (3·45%)	0	3·45
Partial Gastrectomy						
1. Anterior Polya:						
For duodenal ulcer ..	34	8	29	0	0	–
For gastric ulcer	178	116	199	1 (0·5%)	1	1·0
For gastric carcinoma ..	79	48	93	0	0	–
2. Anterior Polya with Entero-anastomosis:						
For duodenal ulcer ..	2	0	1	0	0	–
For gastric ulcer	1	3	2	1	0	–
For gastric carcinoma ..	1	2	3	0	0	–
3. Posterior Polya:						
For duodenal ulcer ..	81	25	77	0	2 X-ray	2·59
For gastric ulcer	267	167	306	0	1	0·3
For gastric carcinoma ..	70	31	80	0	0	–
Gastric ulcer and duodenal ulcer	14	9	18	0	0	–
4. Posterior Polya with Entero-anastomosis:						
For duodenal ulcer ..	0	0	0	0	0	–
For gastric ulcer	0	1	1	0	0	–
For gastric carcinoma ..	0	0	0	0	0	–
5. Billroth No. I:				Gastroduodenal ulceration		
For duodenal ulcer ..	43	12	38	0	8	21·0
For gastric ulcer	80	37	85	2 (2·4%)	1	3·5
For gastric carcinoma ..	26	6	23	0	0	–
6. Old Type Billroth, No. II:				Gastrojejunal ulceration		
For duodenal ulcer ..	3	0	1	1	0	–
For gastric ulcer	15	5	11	0	1	–
For gastric carcinoma ..	15	13	14	0	0	–

* With or without procedures on actual lesions (*excision, infolding, cauterization, etc.*).

SUMMARY: INCIDENCE OF GASTROJEJUNAL ULCER AFTER ALL CASES OF OPERATION *

For Duodenal Ulcer—		
2051 traced cases		
Proved ulcers	.. .. ..	85 (4·14 per cent)
Proved and suspected ulcers	.. ..	176 (8·63 per cent)
For Gastric Ulcer—		
1382 traced cases		
Proved ulcers	.. .. ..	32 (2·32 per cent)
Proved and suspected ulcers	.. ..	62 (4·48 per cent)

The first fact that emerges is that no patient with *carcinoma* developed a secondary ulcer, whatever operation he had undergone. There were 644 such cases, of whom 436 were traced. The possible explanations are: (1) That carcinoma patients are immune from secondary ulceration; (2) That these patients do not live long enough for secondary ulcers to develop—this is only true in part, as secondary ulcers may appear very quickly; (3) Symptoms of secondary ulcer are likely to be masked by those of carcinoma. It is probable that secondary ulceration is a rare event after operation for carcinoma owing to the low acidity and probably also to the diminished peptic activity of the gastric juice.

Of cases of *duodenal ulcer* operated on we find that the incidence of secondary ulcer is just over 4 per cent, taking the cases successfully followed up and the number of secondary ulcers found at subsequent operation. If to these cases we add those where the presence of an ulcer was diagnosed on clinical or radiological evidence only, the incidence rises to over 8 per cent. This is much higher than the 2·8 per cent arrived at by Luff[2] in his investigation into the after-history of gastro-enterostomy, but that figure is clearly an underestimate even of the cases proved by operation; in the list of operations required for 'intercurrent' lesions after gastro-enterostomy for duodenal ulcer, no fewer than four are almost certainly cases of secondary ulcer—indeed, one patient had a gastrocolic fistula, and a similar criticism applies to gastro-enterostomy for pyloric ulcer and for perforated duodenal and pyloric ulcers.

In arriving at a true estimate of the incidence of secondary ulcer we are faced with the difficulty that there is a large number of untraced cases, more than one-third of the total, and it is impossible to know whether the proportion is the same for these untraced cases or not. From experience I am of opinion that it is less, as I believe that most patients return to the same surgeon when symptoms recur. We are also in a difficulty with those cases where the diagnosis rests on symptoms. In some of these the diagnosis is undoubtedly wrong, but in what proportion this is so it is impossible to say.

Taking all things into consideration, I think it is a fair estimate to say that secondary ulcer occurs in about 6 per cent of patients after posterior gastrojejunostomy for duodenal ulcer.

The figures for posterior gastrojejunostomy with entero-anastomosis are too small for any conclusions to be drawn from them, but as they stand they do not support the view that entero-anastomosis adds to the risk.

Anterior gastrojejunostomy seems to carry definitely a higher risk, and anterior

* The nomenclature of the operations in *Table I.* includes the various modes by which they may be carried out and should be interpreted as follows: *Anterior Polya* = partial gastrectomy with antecolic end-to-side anastomosis. *Posterior Polya* = partial gastrectomy with retrocolic end-to-side anastomosis. *Billroth No. I* = partial gastrectomy with gastroduodenal end-to-end anastomosis. *Old type Billroth No. II* = partial gastrectomy with closure of the cut end of the stomach and gastrojejunostomy.

gastro-enterostomy with entero-anastomosis is especially harmful, although the figures again are very small in the latter condition. A study of the published cases many years ago convinced me that the combination of anterior gastro-jejunostomy with entero-anastomosis was a very deadly one, and these figures, small as they are, confirm me in my impression that this operation should not be used in ulcer cases. The small series of cases of gastroduodenostomy merely shows that this operation is not immune from secondary ulcer.

For the rest, it would appear that methods of gastric resection by the Polya methods are very much less liable to secondary ulceration than gastro-enterostomy. The numbers, however, are small, and it may be that a more general adoption of these operations would result in a higher incidence. Certainly further ulceration may and not infrequently does follow Polya gastrectomy for secondary ulcer.

It is difficult to estimate the risks of partial gastrectomy by the Billroth I method, as we have no cases proved by operation, and eight diagnosed on symptoms in a very small series. If the diagnosis is correct in any larger proportion of these, then the incidence is high.

Cases of *gastric ulcer* treated by posterior gastrojejunostomy in the present series developed proved secondary ulcers in 5·32 per cent, and the combined percentage of proved and suspected ulcers is 10·45 per cent. Both these percentages are definitely higher than the corresponding figures for duodenal ulcer patients.

This is a very unexpected finding, and one which is quite contrary to my personal experience. I believe that the explanation lies in the custom of including ulcers of the pyloric region among the gastric ulcers. I suspect that in a very large proportion of these cases the original lesion was a pyloric ulcer, i.e., one of the same nature as a duodenal ulcer, and which would be classified as duodenal by many surgeons. This view is supported by the fact that if we take the percentage incidence of all the post-duodenal cases, including all types of operation, we find that in 2051 traced cases there were 83 proved and 91 suspected secondary ulcers, viz., 4·05 per cent and 8·5 per cent—almost exactly the same as that for posterior gastro-enterostomy. For the post-gastric ulcer cases the corresponding figures are, total 1382, proved ulcers 33, suspected ulcer 30, giving 2·38 per cent and 4·55 per cent. Thus the percentage incidence over all operations is only about half that after posterior gastrojejunostomy for gastric ulcer.

Where other operations are concerned, such as gastrojejunostomy plus excision of ulcer, gastric resections, etc., the original ulcer was obviously of the true lesser-curve or gastric type, and the incidence of secondary ulceration is therefore small.

Other suggestive facts are found when a similar problem arises in connection with cases stated to have followed operation for gastric ulcer in the analysis of the returns of individual instances of secondary ulcer in *Tables II–VI*. It is convenient to deal with these facts here as the problem is the same. In 107 cases the original ulcer was said to be gastric, but of those 14 were definitely called pyloric and in 13 the operation was done at the time of an acute perforating ulcer, which must obviously have been situated at the pylorus to call for such an operation. In two more the operation was done some years after an acute perforation. This makes a total of 29 out of 107 where the ulcer was almost certainly pyloric, and probably others were of the same kind.

It seems probable, therefore, that in a considerable proportion of cases where the original ulcer was labelled gastric it was really pyloric or duodenal.

It is to be noted that a large proportion of gastric resection operations were for gastric ulcer and that the incidence of proved secondary ulcer is very small.

In 622 resection operations (including local excision and gastrojejunostomy) for gastric ulcer there were 4 proved examples of secondary ulceration and 4 suspected, viz., 0·65 per cent proved and 1·30 per cent combined. In 146 for duodenal ulcer there were 1 proved case and 8 suspected. This gives 0·68 per cent proved cases and 7·5 per cent combined. The notable feature is the high incidence of suspected cases after operation for duodenal ulcer. The highest incidence after resection operations seems to be after operations of the Billroth I type.

Turning now to the analysis of actual cases of secondary ulcer, including cases of lesser-curve ulcer developing after operation for ulcer, we find 458 cases, after rejecting several where it seemed probable that the lesion was not a secondary ulcer, but an unhealed or recurrent gastric lesion: 107 of these followed operation for gastric ulcer, and I have already dealt with the question as to a possible fallacy in this figure. The men outnumber the women by about 3½ to 1, and the condition is met with chiefly between the ages of 30 and 60, the peak incidence being the decade 40–50 (*Table II*).

Table II.—Age and Sex Incidence in Gastric Ulcer

			Males	Females
		Under 20 years ..	0	0
		20–30 years ..	4	3
		30–40 years ..	25	2
Males ..	82	40–50 years ..	35	10
Females ..	24	50–60 years ..	14	6
Not stated ..	1	60–70 years ..	4	3
	107	70–80 years ..	0	0
			82	24
		Not stated ..	1	

In comparison with the above, there were 351 cases where the primary operation was for duodenal ulcer. The chief difference between the two is the enormous disparity in the sex incidence in the latter, men outnumbering women by 21½ to 1. There is not much difference in the age except that the proportion of cases under 30 is somewhat greater (*Table III*).

Table III.—Age and Sex Incidence in Duodenal Ulcer

			Males	Females
		Under 20 years ..	1	1
		20–30 years ..	45	1
		30–40 years ..	91	2
		40–50 years ..	117	9
Males ..	328	50–60 years ..	59	1
Females ..	16	60–70 years ..	12	0
Not stated ..	7	70–80 years ..	3	0
	351		328	14
			14	
		Add 9 cases, age not stated ..	9	
		Stated ..	351	

The *type of the original operation* (*Tables IV, V*) was simple posterior gastrojejunostomy in a very large majority of cases, and the chief difference to be noted

between the post-gastric and the post-duodenal series is that the original operation was a partial gastrectomy of some kind in 8 out of 107 in the former and in only 1 out of 351 in the latter. This is of course explained by more common use of these procedures in cases of gastric ulcer. In the same way we account for the primary operation of gastrojejunostomy in combination with local excision or cautery of an ulcer. Entero-anastomosis figured in about $4\frac{1}{2}$ per cent and pyloric occlusion in about 4 per cent.

Table IV.—Type of Original Operation in Cases of Gastrojejunal Ulcer Following Operation for Gastric Ulcer

Posterior gastrojejunostomy	77
Posterior gastrojejunostomy with excision of ulcer	7
Posterior gastrojejunostomy with cautery of ulcer	4
Posterior gastrojejunostomy with pyloric occlusion	2
Posterior gastrojejunostomy with entero-anastomosis	3
Anterior gastrojejunostomy	6
Posterior Polya gastrectomy	2
Anterior Polya gastrectomy	2
Billroth I	1
Billroth II	1
Not stated	2
	107

Table V.—Type of Original Operation in Cases of Gastrojejunal Ulcer Following Operation for Duodenal Ulcer

Posterior gastrojejunostomy	315
Posterior gastrojejunostomy with pyloric occlusion	10
Posterior gastrojejunostomy with entero-anastomosis	4
As above and pyloric exclusion	1
Anterior gastrojejunostomy	12
Anterior gastrojejunostomy with entero-anastomosis	8
Billroth II	1
	351

It is frequently stated that gastrojejunostomy done at the time of an acute perforation is especially liable to secondary ulceration. From an examination of this series I find that in 351 gastro-enterostomies for duodenal ulcer the operation was done at the time of an acute perforation in 39—about 11 per cent. These findings support the view that secondary ulceration is specially apt to follow such a proceeding. In a further 13 instances the operation was done some time after suture of a perforation, so that perforation figures in 52 out of the 351 cases (*Table VI*).

Table VI.—Gastrojejunal Ulcer Following Operation for Perforation

Primary operation done at the time of perforation.—	
a. Perforated gastric ulcer	13
b. Perforated duodenal ulcer	39
	52

That is, 11 per cent of the total of 458 cases.

In 15 cases the primary operation was done at some period after an acute perforation. Therefore in 67 cases the original ulcer was a perforating one—14·6 per cent.

I have already stated that in the post-gastric ulcer series the operation was done for acute perforated ulcer on 13 occasions—just over 12 per cent—and on 2 occasions at some period subsequent to perforation. In the total of 458 secondary ulcers, therefore, the primary operation was done for acute perforation in 52—a

little over 11 per cent. On 15 occasions it was done at some period subsequent to perforation, giving a total of 67 cases in which perforation figured in the original lesion, or 14·6 per cent.

It is sometimes stated that when pyloric stenosis has supervened the liability to secondary ulceration is lessened, though anyone who has studied the early recorded cases would know that this is not so. As the information was not asked for in this inquiry, no conclusions can be drawn from the fact that it was mentioned as being present in 7 cases only.

SYMPTOMS (*Table VII*)

Pain* is the cardinal symptom of secondary ulcer. It is even more prominent than in ordinary gastric or duodenal ulcer, and is frequently more intense. It differs also in situation. It may be felt almost anywhere in the abdomen, either on the right side or the left, above or below the umbilicus, though in a very large proportion it is felt in the epigastric region, and when it is located to one side it is usually the left. In many patients the pain radiates over a wide area, being felt in several of the regions described. A curious feature is the relatively large number of cases in which the lower abdomen is affected.

A further point which emerges is that pain is seldom absent. In only 20 of the 458 cases was it definitely stated that pain was absent, and 14 of these were cases of colic fistula. I shall refer to this last point again.

The pain is usually severe in character, and does not exhibit the same precise features that it does in ordinary gastric or duodenal ulcer. Sometimes it is described as being continuous. The relationship to food is not so constant, but when present the onset is usually late, though this varies widely. Relief from ingestion of food is not very constant, but vomiting usually seems to give relief, so much so that in a fair number of cases it is said the patient induces vomiting in order to relieve the pain.

Vomiting occurred in half the cases. It relieved the pain, was sometimes self-induced, and varied much in frequency and intensity. The two conditions in which it was severe were when there was stenosis at the anastomosis and when a fistula into the colon existed. In the latter case the vomiting was often fæcal.

Diarrhœa was noted in 55 cases, and many of these were patients with colic fistula. So far from being common, it is definitely stated to have been absent in 319 cases, and many of the reporters have gone out of their way to say that instead of suffering from diarrhœa, the patients have had extreme constipation. Where colic fistula existed, however, diarrhœa, often extreme, has been a constant symptom.

Wasting was more often met with than diarrhœa—in almost half the cases, but again it is a symptom which is especially in evidence where colic fistula exists.

Hæmorrhage occurred in 124 patients, and in 65 of these it was severe or repeated. It manifested itself both in the form of hæmatemesis and melæna, and figures as the actual cause of death in 9 cases: 2 of these are obvious

* In many cases the pain is described as widespread, extending from the upper to the lower abdomen. It is to be noted that the pain was stated to be in the left side in 93 cases and in the right in 24 only. It is also to be noted that of the 20 cases in which it was definitely stated that there was no pain, 14 were cases of fistula into the colon.

Table VII.—Symptoms and Signs in Gastrojejunal Ulceration Following Operation for Duodenal and Gastric Ulcer

Pain—	
Epigastric	245
Right epigastric	11
Left epigastric	44
Right hypochondrium	9
Left hypochondrium	20
Umbilical	23
Left flank	4
Lower abdomen	41
Left iliac fossa	25
Right iliac fossa	4
In the back	13
None	20
Not stated	14
Type of Pain—	
Continuous	13
Not related to food	69
Onset within half-hour after food	50
Onset ½–1 hour after food	50
Onser 1–2 hours after food	80
Onset more than 2 hours after food	67
Pain relieved by food	74
Not relieved	4
Night pain	46
Type of pain not specified	64
Vomiting (based on 411 cases, acute perforations excluded)—	
Present	229
Absent	157
Not stated	25
Diarrhœa—	
Present	55
Absent	319
Not stated	37
Hæmorrhage—	
Slight	59
Severe	65
Absent	265
Not stated	22
Wasting—	
Present	166
Absent	198
Not stated	47
Tenderness—	
Epigastric	145
Right epigastric	12
Left epigastric	45
Right hypochondrium	8
Left hypochondrium	9
Umbilical	12
Left umbilical	31
Right umbilical	6
Left iliac fossa	4
None	68
Not stated	118

Palpable lump noted in 22 cases only, and in only 7 of these had the original operation been anterior gastrojejunostomy.

post-operative bleedings, but 7 occurred at intervals of three weeks to several years after operation, and are genuine examples of bleeding from a secondary ulcer. The only other symptom of any note is anæmia after severe or repeated hæmorrhage.

Tenderness on Palpation was present in more than half the cases. Generally it was elicited in the epigastrium, but it is noteworthy that it was found in almost every region of the abdomen. The left side of the abdomen was implicated much more commonly than the right side, and this preference for the left is more definite as regards tenderness than pain. Speaking generally, both pain and tenderness seem to be met over a much wider distribution than in primary duodenal or gastric ulcer.

It is somewhat surprising to find that a palpable lump was found on 22 occasions only, and that of these the primary operation was of the anterior type only in 7. This is very different from the reports of cases years ago, when a palpable tender lump under the left rectus muscle was commonly described and figured as an important point in the diagnosis. It is of course a fact that in the early days anterior gastrojejunostomy was much the commoner operation, and perforation into the abdominal wall tends to happen in secondary ulceration after this operation.

In this series there were only 28 cases of pre-colic operations, including 2 examples of anterior Polya gastrectomy, and of these 6 had acute perforating ulcers. There remain, therefore, 22 cases, in 7 of which a palpable lump was noted, roughly one-third. This confirms the old observation that a palpable mass is common after an anterior operation and rare after a posterior one, which is only what is to be expected when the deep situation of the posterior operation is remembered.

RADIOLOGICAL FINDINGS

Radiological investigation was carried out in 279 cases, and in these the findings were positive in 184, doubtful in 29, and negative in 66 (*Table VIII*).

Table VIII.—Radiological Investigations in 407 Cases of Gastrojejunal Ulcer (Acute Perforations Excluded)

No examination in	128
Negative findings	66
Doubtful findings	29
Positive findings	184
	407

Where details were given the positive diagnoses were made on the following appearances, or combinations of them:—

Delay in emptying the stomach ..	20
Tenderness at the stoma	19
Residue at the stoma	25
Deformity at the stoma	17
Stenosis of the stoma	13
Crater	25
Gastrocolic fistula	25
Deformity in the jejunum	4
Ulcer of the stomach	7

In one case a Murphy's button was seen in the stoma.

ETIOLOGY OF SECONDARY ULCER (*Tables IX–XIII*)

We are no nearer solving the cause of secondary ulcer than we were twenty-five years ago, but our ideas are modified in some respects. At that time it was supposed that errors in technique were of great importance, and numerous suggestions were put forward, such as the use of a continuous unabsorbable suture, the pressure of clamps, the production of a hæmatoma in suturing, and in a general way sepsis of the anastomosis from lack of care in the suturing. Paterson thought that errors in technique probably were responsible for his gastrojejunal form of ulceration, but not for the true jejunal ulcers. An argument in favour of these views of the influence of technique was that the ulcers generally came within the first two years after the operation.

In our series we find that the onset of symptoms was within two years in 284 out of 458 cases—that is, just over 62 per cent (*Table IX*). This does not seem to me to favour the view that technique is a large factor in the production of secondary ulcer, as in such a large proportion the onset is so delayed that it is difficult to believe that technique can have had any influence. The shortest period was nine days in a patient who had a subacute perforation, and in 47 patients the interval which elapsed was less than one month. This suggests that in some cases at least technique has been at fault, but when we try to find any particular error there is none which can be found in any very large number of cases.

Table IX.—Period after Original Operation for Duodenal or Gastric Ulcer at which Symptoms of Gastrojejunal Ulcer Began (458 Cases)

Less than one month	47	5–6 years	15
1–3 months	40	6–7 years	10
3–6 months	61	7–8 years	8
6–12 months	70	8–9 years	5
1–2 years	66	9–10 years	9
2–3 years	36	Over 10 years	15
3–4 years	30	Not stated	29
4–5 years	17		

Thus in 109 cases more than three years elapsed before the onset of symptoms, roughly 25 per cent of the cases where the information was available. The shortest period was 9 days.

Table X.—Interval between Original Operation for Duodenal or Gastric Ulcer and First Operation for Gastrojejunal Ulcer (458 Cases)

Less than one month	5	5–6 years	28
1–3 years	6	6–7 years	27
3–6 months	12	7–8 years	15
6–12 months	39	8–9 years	19
1–2 years	90	9–10 years	13
2–3 years	63	Over 10 years	38
3–4 years	36	Not stated	26
4–5 years	41		

Unabsorbable suture material, which I myself at one time blamed, was found on 28 occasions in the 279 cases where the information was available—about 10 per cent—and it is interesting to note that in one of these catgut was still unabsorbed at the end of two and a half years. On 3 occasions a metallic foreign body was present, one being a Murphy's button. The mere presence of unabsorbed suture material is not proof that it was the cause of the ulceration. If present, it would

naturally be exposed during the process of ulceration. If this were really a frequent cause of secondary ulcer, one would expect that the use of absorbable sutures would materially lessen the risk, but we find that in a series of 272 where the technique was given, in 214 catgut alone was employed. The use of an absorbable suture is therefore no safeguard against secondary ulcer.

There are only 9 cases where clamps were dispensed with (*Table XI*), but in view of the very general use of clamps I do not think too much stress can be laid on this fact. I have myself for some years avoided the use of a clamp on the jejunum because I found that if it was applied sufficiently tightly to control the bleeding it was apt to bruise the bowel.

Freak happenings, like the presence of a Murphy's button, need not be considered, as few surgeons would employ such a technique nowadays.

It seems difficult, then, to point to any particular error in technique which can be blamed as a common cause of secondary ulcer, though probably it is a secondary factor in some cases.

Table XI.—TECHNIQUE EMPLOYED IN ORIGINAL OPERATION FOR GASTRIC OR DUODENAL ULCER

Clamps and continuous catgut suture both rows	210
Clamps and continuous catgut inner layer, with continuous silk or thread outer layer	45
Clamps and continuous silk or thread both layers	7
Clamps, interrupted catgut and thread	1
No clamps and continuous catgut both layers	4
No clamps and continuous catgut inner layer with continuous silk or thread outer layer	5
Murphy's button	1
Not known	185
	458

Table XII.—SUTURE MATERIAL OF ORIGINAL OPERATION AT TIME OF SECONDARY OPERATION

Absent	246
Present (in one case catgut after 2·5 years)	28
Piece of needle	1
Piece of steel	1
Murphy's button	1
Not stated	181
	458

That the production of these ulcers depends in some way on the action of the gastric juice is agreed on all hands. Paterson made a very able special plea for hyperacidity as the chief cause, but this does not seem to me to be in accordance with the facts, even those on which he based his opinion. In our series hyperacidity was present in only about half the cases when investigations were made, and in 8 cases there was actual achlorhydria (*Table XIII*).

Although we may agree that hyperacidity is a common accompaniment of secondary ulcer, it is difficult to believe, in view of these findings, that it is the actual cause. It may indeed be the result. Even if we accept it as the cause, we are not much better off, because we are still in the dark as to the cause of the hyperchlorhydria.

That the gastric juice is essential in the production of these ulcers is, however, certain. The experimental work of Matthews and Dragstedt,[3] who exposed the mucosa of the small intestine to the action of unneutralized gastric juice, shows

conclusively that in such conditions chronic peptic ulcer follows inevitably. Their work also shows the importance of concentration of the gastric juice and the influence of stasis in increasing that concentration, and confirms the value of reflux of bile and pancreatic juice in neutralizing the gastric juice, an observation made many years ago by Boldyreff and confirmed by Paterson, who believes this to be the chief physiological action of gastrojejunostomy. Owing to the ease of estimating it the acidity of the gastric juice has attracted much more attention than the peptic activity, but it is well to remember that the latter is inactivated by the action of bile and pancreatic juice, just as the former is neutralized.

Table XIII.—CONDITION OF GASTRIC JUICE IN GASTROJEJUNAL ULCER

The acidity of the stomach contents after a test-meal was estimated in 138 cases as follows :—

Hyperchlorhydria	64
High normal acidity	12
Medium normal acidity	27
Low normal acidity	27
Achlorhydria	8

The normal range of free HCl is taken as 20–40.

Similar investigations at the time of the primary operation in 66 cases gave the following results :—

Hyperchlorhydria	32
Normal acidity	31
Achlorhydria	3

It can be agreed, therefore, that gastric juice is essential for the production of chronic secondary ulcer, and that its noxious influence is greatly increased by any stagnation or interference with its exit from the stomach or anything which prevents the reflux of bile and pancreatic juice. For these reasons the gastro-enterostomy should be well placed and of sufficiently large size. If it is too much towards the cardiac end, it will probably not empty the stomach very efficiently. Caution must, however, be used in deciding that the gastro-enterostomy opening has been too small originally. The presence of secondary ulceration on the anastomosis leads to considerable contraction of the stoma, so that an opening which was originally quite large becomes small and inadequate.

Operations en-Y and with entero-anastomosis should not be employed in the treatment of ulcer cases, either as primary or secondary operations, since they expose the jejunal mucosa to unneutralized gastric juice. The true etiology is unlikely to be known until we have solved that of duodenal and gastric ulcer. Whatever that cause, it is probably still active in the case of secondary ulcer.

MORBID ANATOMY

The information received was not sufficiently detailed to enable me to give anything but a broad general description of the lesions found.

Site of Gastrojejunal Ulcer (*Table XIV*).—The first point which emerges is the enormous preponderance of anastomotic ulcers—285, as against 99 jejunal ulcers. There was not enough detail to allow me to give the exact location of the ulcers on the anastomosis, but it is evident that sometimes the ulceration extends right round the anastomotic ring. When it is more limited it tends to exist at the

angles, and in my own experience I have found that the proximal angle of the anastomosis is a favourite site. I had an impression that jejunal ulcer was more likely to follow anterior gastrojejunostomy, and anastomotic ulcer the posterior operation, but that is not the case. True jejunal ulceration is found in the efferent loop in the great majority of cases. It may be situated within ½ in. of the anastomotic ring or 1 to 2 in. or more away from it. The situation in the afferent loop

Table XIV.—SITE OF GASTROJEJUNAL ULCER * (458 CASES)

Anastomotic	285
Jejunal, exact site not stated	6
Jejunal. Afferent loop	14
Jejunal. Efferent loop	68
Jejunal. Mesenteric border	11
Gastric. Near anastomosis	1
Gastric. Extending from anastomosis	30
Jejunal. Extending from anastomosis	14
Anastomotic and lesser curve ulcer	11
Anastomotic and separate jejunal ulcer	1
Independent ulcer lesser curve	5
Situation not stated	12

* This refers only to the ulcer operated on by the reporter of the case.

is quite rare. An interesting group of cases is that in which a jejunal ulcer is found on the mesenteric border of the bowel, directly opposite the stoma of the gastro-enterostomy. This is usually quite independent of the anastomosis, and may produce obstruction by contraction drawing up a spur of bowel into the stoma. An ulcer was found in this situation on 11 occasions, so that it is a rare variety.

Complications (*Table XV*).—Perforation of a secondary ulcer may be acute into the general peritoneal cavity, or chronic. After an anterior gastro-enterostomy the secondary ulcer tends to become adherent to the anterior abdominal wall and to penetrate the rectus sheath, giving rise to a tender mass. In neglected cases the perforation may extend through the anterior abdominal wall and give rise to an external fistula.

Table XV.—COMPLICATIONS OF GASTROJEJUNAL ULCER

Acute perforation	51
Fistula into colon	40
Perforation into abdominal wall	16
Perforation into mesocolon	21

After posterior operations there is a tendency to chronic perforation into the mesocolon, and the latter becomes thickened and contracted. In this way the colon becomes pulled down and held tightly against the thickened ulcer. In course of time a fistula may form between the two. This happened in 40 cases in the series. The fistula may be between the stomach and the colon—gastro-colic fistula; between the anastomosis and the colon—gastro-jejunocolic fistula; or between the jejunum and the colon—jejuno-colic fistula. After a fistulous opening has become well established, there is a tendency for the ulceration to heal, a fact to which I I shall revert later.

In certain cases the ulceration spreads from the anastomosis to the stomach on the one hand or the jejunum on the other. Thus we find extension to the stomach in 30 cases and to the jejunum in 14. The extension from the

anastomosis may be over a long extent, and *Fig.* 291 shows a picture of a lesser-curve ulcer of the stomach connected to the anastomosis by a track of ulceration. It is said that all roads lead to Rome, and this shows the tendency of gastric ulceration to make for the lesser curve.

In 11 patients anastomotic ulcer and an independent lesser-curve ulcer existed together, but 8 of these followed operation for gastric ulcer and are probably examples of unhealed or recurrent ulcers. In the other 3 the gastric and anastomotic ulcers are both post-operative. These cases represent an intermediate stage on the way to the following type, where an independent ulcer formed on the lesser curve after gastrojejunostomy for duodenal ulcer. This has happened on 5 occasions in the present series. I have been aware of this possibility for a good

FIG. 291.—Lesser-curve ulcer of the stomach connected to the anastomosis by a track of ulceration.

many years now. Though at first I thought it was an accidental occurrence, yet it influenced my views on the value of gastro-enterostomy as a treatment for lesser-curve ulcer. I have now seen a sufficient number of cases to convince me that the development of a lesser-curve ulcer after gastro-enterostomy for duodenal ulcer or pyloric stenosis is a phase of secondary ulceration. I would liken these ulcers to those on the mesenteric border of the jejunum. Usually they are situated directly opposite the stoma, though occasionally they are higher up. Further evidence of the formation of these ulcers after gastro-enterostomy is to be found from a study of Luff's paper, to which I have already referred. He reports 3 cases of lesser-curve ulcer after gastro-enterostomy in a series of 744 cases of operation for duodenal ulcer, and 2 cases in 454 similar operations for pyloric ulcer.

I have very little doubt that the alteration in the physiology of the stomach in some way leads to an increased liability to ulceration of the lesser curve.

TREATMENT OF SECONDARY ULCER

In spite of the fact that in many of these patients a secondary ulcer may exist for years, the majority are so miserable and the symptoms are so little relieved by medical treatment that resort to operative measures becomes imperative. Acute perforation of course demands immediate intervention, and repeated hæmorrhage is another indication for operation. In most cases, however, operation is demanded for the relief of the constant intolerable pain. The operations may be classified as follows :—

1. **Local Operations** (*Table XVI*).—For the most part these are unsatisfactory, most of the patients being unrelieved and many requiring further operations. It is interesting to note that when the operation is confined to removal of a silk suture, no relief was obtained.

Table XVI.—Local Attack on Ulcer, with or without Plastic Operation on the Stoma

Excision—	
Good	5
Fair	1
Symptoms not relieved	5
Further operation	17
Late result not known	14
Died	3
Died later	2
	47
Excision of Affected Loop of Jejunum—	
Good	1
Fair	0
Symptoms not relieved (died later of 'cancer')	1
Further operation	1
Late result not known	2
Died	1
	6
Transgastric Cautery of Ulcer—	
Good	2
Further operation	2
Late result not known	2
Died	0
	6
Removal of Murphy's Button—	
Good result	1
Removal of Silk—	
Not relieved	2
Local Excision of Lesser-curve Ulcer—	
Late result not known	1
Further operation	1

2. **Reconstitution of the Normal Alimentary Passage** (*Table XVII*).—Under this heading proceedings of widely different severity are included. In its simplest form it consists of the undoing of the gastro-enterostomy and the closure of the openings in the stomach and jejunum. In others it includes a resection of the affected loop of jejunum with end-to-end or lateral anastomosis. In one case the upper end of the jejunum was closed and the continuity of the alimentary canal re-established by anastomosing the lower end of the jejunum to the third part of the duodenum. This operation of restoration to the normal is a formidable

one and involves what is really the most difficult part of any operation for secondary ulcer—the freeing of the anastomosis from the mesocolon. It carries with it, therefore, a fairly high mortality. The results are disappointing. In only about 20 per cent was a known cure obtained, while 12 per cent required further operation, and one case died as the result of a perforation of a duodenal ulcer later. In 14 per cent the symptoms were unrelieved. The trouble is, of course, that the original duodenal ulcer tends to recur. The operation is only suitable for cases with a widely patent pylorus and duodenum, and should be reserved for those in whom no scar, or only a very slight one, is present in the duodenum.

Table XVII.—Reconstitution of Normal Alimentary Passage

Simple Undoing of Gastro-enterostomy and Re-constitution—		
Good	18	
Fair	7	
Unrelieved	13	
Further operation	11	
Late result not known	30	
Died	11	
Died later of perforation	1	
		91
Excision of Gastrojejunostomy with Gastroduodenostomy or Pyloroplasty—		
Good	5	
Fair	1	
Unrelieved	3	
Further operation	2	
Late result not known	4	
Died	0	
		15
Finney's Pyloroplasty—		
Not traced	1	
Gastroduodenostomy—		
Recovered	1	
Died	1	
Pyloric Occlusion—		
Further operation necessary	1	

Where an active duodenal ulcer still exists, or where the duodenum is stenosed, the operation must be combined with gastroduodenostomy or some form of pyloroplasty. This operation is spoken of highly by some, but the numbers in the present list are too small for a definite opinion to be formed. It is noteworthy, however, that one-third of the patients were unrelieved or required a further operation.

3. **New Gastro-enterostomy** (*Table XVIII*).—Under this heading are included cases where the old gastro-enterostomy has been resected and resutured, an extension of the first type of operation, and those where after resection and closure of the old gastro-enterostomy an entirely new one has been established.

Table XVIII.—New Gastrojejunostomy

New Posterior Gastrojejunostomy—		
Good	3	
Fair	1	
Unrelieved	1	
Further operation	4	
Late result not known	3	
Died	6	
		18

New Posterior Gastrojejunostomy with Entero-anastomosis—	
Good	2
Fair	0
Unrelieved	3
Further operation	3
Late result not known	4
Died	2
Died later	4
	18
New Anterior Gastrojejunostomy—	
Good	5
Fair	0
Unrelieved	0
Further operation	3
Late result not known	6
Died	0
Died later	1
	15
New Anterior Gastrojejunostomy with Entero-anastomosis—	
Good	1
Fair	0
Unrelieved	0
Further operation	0
Late result not known	2
Died	1
	4

Finally, in a few cases a new anastomosis has been done, leaving the old one intact. It will be noted that there was an operative mortality of 16 per cent and that quite a number of patients died later, especially in the series of new posterior gastrojejunostomy with entero-anastomosis. The percentage of good ultimate results is only 20.

4. **Entero-anastomosis** (*Table XIX*).—This was only rarely done and has nothing to recommend it in the small series. It offends against all our ideas on the causation of secondary ulcer.

Table XIX.—ENTERO-ANASTOMOSIS

Good	2
Unrelieved	1
Further operation	2
Late result not known	3
Died	2
Died later of hæmorrhage	1
	11

5. **Various Methods of Gastrectomy** (*Table XX*).—These operations offer by far the best chance of a cure—about 60 per cent, which is much higher than any other form of operative treatment. As against this, the operative mortality is very high, especially after the *posterior Polya operations*, when it approximates to 20 per cent. The *anterior Polya operation* shows a lower mortality—15·5 per cent—but the results are not quite so good as those from the posterior operation, 1 patient dying later and 3 requiring a further operation. I cannot help feeling that the mortality from these operations should be reduced. The difficult and dangerous part of the operation is that which is shared by all procedures which interfere with the anastomosis, i.e., the freeing of the anastomosis from the mesocolon and the resection of the anastomosis. When this has been accomplished the resulting gastrectomy is easy.

If recurrence takes place after a *partial gastrectomy* operation, any further operative treatment becomes most difficult and dangerous. In order to minimize the possibility of this, a gastrectomy for secondary ulcer should be made as high as possible.

Table XX.—Gastrectomy by Various Methods

Posterior Polya Gastrectomy—		
Good	49	
Fair	4	
Unrelieved	2	
Further operation	3	
Late result not known	7	
Died	16	
		81
Posterior Polya with Entero-anastomosis—		
Good	0	
Fair	0	
Unrelieved	2	
Further operation	1	
Late result not known	4	
Died	0	
		7
Anterior Polya Gastrectomy—		
Good	25	
Fair	1	
Unrelieved	0	
Further operation	3	
Late result not known	8	
Died	7	
Died later	1	
		45
Polya Gastrectomy (type not stated)—		
Good	8	
Fair	3	
Unrelieved	1	
Further operation	0	
Late result not known	4	
Died	4	
		20
Partial Gastrectomy (type not stated)—		
Good	0	
Fair	1	
Unrelieved	0	
Further operation	2	
Late result not known	3	
Died	2	
		8
Billroth No. I—		
Good	1	
Fair	0	
Unrelieved	0	
Further operation	1	
Late result not known	3	
Died	0	
		5

6. **Devine's Operation** (*Table XXI*).—Devine's operation of unilateral exclusion, which consists of a division of the stomach above the anastomosis, closure of the lower end, and anastomosis of the upper end to the side of the jejunum,

offers an easier alternative to partial gastrectomy. This was used in only 2 cases in the present series. In principle there seems to be no reason why it should not prove eminently successful.

Table XXI.—DEVINE'S OPERATION

Good result	1
Not traced	1
	2

7. **Laparotomy** (*Table XXII*).—One feature is the number of patients in whom an exploratory laparotomy was the first of the secondary operations. These operations usually ended in the breaking down of adhesions, and it is not surprising that the results were almost uniformly unsatisfactory, and that most of the patients underwent further operations subsequently.

Table XXII.—LAPAROTOMY

Good	1
Fair	1
Unrelieved	3
Further operation	11
Died	1
	17

8. **Operations Impossible to Classify.**—These are summarized in *Table XXIII*.

Table XXIII.—VARIOUS OPERATIONS IMPOSSIBLE TO CLASSIFY

Ligature of vessels—2 cases requiring further operation.
Jejunostomy—4 cases: 3 died, 1 not traced.
Excision of duodenal ulcer for hæmorrhage—1 case requiring further operation.

Nature of Operation not Stated—

Good	1
Unrelieved	3
Further operation	3
Died	2
	9

In Addition, the Following Operations were Done—

Closure of perforated duodenal ulcer	2
Decapsulation of the kidney	1
Removal of cystic ovary	1
For appendix abscess	1
Cautery of gastric ulcer	2
Pylorectomy for lesser-curve ulcer	1

SUMMARY OF GENERAL RESULTS OF OPERATIVE TREATMENT IN SECONDARY ULCERATION

The study of *Table XXIV* is a truly saddening experience and one which reveals this complication as a really black spot in surgery. It shows that at the first attempt a reasonably good result was obtained in 31 per cent, but that 16 per cent required further operation, while almost as many died as the result of operation. In addition 12 patients died later as the result of the ulceration. Of the 76 patients who required further operation or operations I have tabulated the results to the present time. It will be seen that while about half of these have been restored to reasonable health, a further 18 died. From a combination of the two tables we

find that in 39 per cent there is a reasonably good result, while in more than 9 per cent the symptoms are known to be still present. Counting operative deaths and those who died from secondary ulcer though not as a result of operation, there were 104 deaths. This means that 22·7 per cent of patients suffering from secondary ulcer are known to have died as the result. The complication of secondary ulceration is therefore a truly disastrous one.

Table XXIV.—Results of Operative Treatment of Secondary Ulcer

1. *Results of First Secondary Operation*—	
Good	120
Fair	23
Still symptoms	34
Required further operation	76
Not known	118
Died from operation	73
Died later	12
	456
2. *Results in the 76 Cases After Further Operations*—	
Good	30
Fair	6
Still symptoms	10
Not traced	12
Died	18
	76
3. *Combination of 1 and 2 in the General Results*—	
Good	150
Fair	29
Symptoms still present	44
Later results unknown	130
Died as result of operation	91
Died of the disease	12
	456

In addition 1 patient died of acute perforation before operation could be done, and 1 case was discovered at a post-mortem for an intercurrent disease.

ACUTE PERFORATING SECONDARY ULCER (*Table XXV*)

Of the 458 cases there were 48 in which the first secondary ulcer was met with as an acute perforation into the general peritoneal cavity. In 42 of these the primary operation had been posterior. Since of the total of 458 cases the primary operation was posterior in 430, this gives a percentage of 9·7. In the remaining 6 the primary operation was of the anterior type. As there were only 28 in which this was the case, the percentage of acute perforations is about 21. From this it would appear that secondary ulcers after an anterior primary operation are more liable to be of the acute perforating type than those following a posterior operation. In addition to the cases which first presented themselves as acute perforations, there were 12 patients in whom an acute perforation occurred at some period after an operation for secondary ulcer, giving a total of 60 cases to be considered.

In 48 the operation consisted of suture of the perforation, with or without drainage of the peritoneum. Of these, 11 died—almost 25 per cent—and only a very small number recovered to be free from symptoms. In 15 further operation proved necessary later.

In 4 patients drainage of the peritoneum only was the operative treatment adopted. As was to be expected, the mortality was 100 per cent.

In a small number of cases entero-anastomosis was done at the time of the suture of the perforation. These were not followed up properly, but on general principles the operation is a bad one.

In 2 patients restoration to the normal alimentary passage was done at the time of the perforation. One died and one had recurrence of symptoms.

The operation of choice is undoubtedly simple suture of the perforation, with or without drainage of the peritoneum according to circumstances. Many will require further operative treatment, but a trial should be made of prolonged dietetic treatment after this simple operation.

Table XXV.—Operations for Acute Perforations

Suture with or without Drainage—	
Good	5
Fair	3
Symptoms recurred	6
Further operation	15
Not traced	8
Died	11
	48
Drainage Only—	
Died	4
Closure of Perforation and Entero-anastomosis—	
Fair result	1
Further operation	1
Later result not known	3
	5
Closure of Perforation and Reconstitution of Normal Passage—	
Symptoms recurred	1
Died	1
	2
Died without Operation	1

GASTROCOLIC FISTULA

Fistula into the colon was present when the patient sought treatment in 40 cases—34 in the post-duodenal series and 6 in the post-gastric. In all of these the primary operation was of the posterior type, but it is noteworthy that in addition to these there were 8 examples of colic fistula following operation for secondary ulcer, and in 2 of these the condition followed an anterior Polya gastrectomy. In both these the fistula was of the jejunocolic type and obviously formed at the place where the jejunum crossed the colon. These two examples are the only cases I have ever known to develop a colonic fistula after an antecolic operation, and it would seem to be due to the peculiarly intimate relationship of the jejunum to the colon after an anterior Polya operation. Cases following gastrojejunostomy have invariably been after the retrocolic operation.

Symptoms (*Table XXVI*).—The symptoms of gastrocolic fistula differ in several important respects from those of ordinary secondary ulcer.

While *pain* is the cardinal symptom of ordinary secondary ulcer it was completely absent in 15 of the 40 cases, and slight only in 8. Thus in 23, or more than

half the cases, pain was a negligible symptom. In only 13 was pain noted as a symptom of any prominence, and in only 4 of these was it said to be severe. No note was made in 4. In one patient the observer stated that pain was a prominent symptom for four years from the time of the original operation, but that suddenly with the onset of fæcal vomiting, diarrhœa, and wasting the pain ceased.

I believe the explanation of this absence of pain is the healing of the active ulceration after the establishment of a fistula into the colon. I have noted at operation on such a case that the very wide communication between the anastomosis and the colon was completely healed and covered with mucosa.

The trilogy of symptoms on which the diagnosis rests is *vomiting, diarrhœa, and wasting*, all three or some of which are invariably present. When the vomiting is fæcal in type the diagnosis is easy, and even when this is not the case the patient frequently complains of foul eructations.

Table XXVI.—Symptoms in Gastrocolic Fistula

Pain—	
Absent	15
Slight	8
Present	9
Severe	4
Not noted	4
	40
Vomiting—	
Fæcal	11
Severe	10
Present	9
Absent	5
Not stated	5
	40
Diarrhœa—	
Severe	18
Present	16
Absent	4
Not stated	2
	40
Wasting—	
Severe	11
Present	19
None	6
Not stated	4
	40

Treatment (*Table XXVII*).—Operative treatment is urgently necessary in this condition. Even though the patient may be free from pain, his condition is miserable and clamorous for relief.

It will be seen that the operative procedures are similar to those adopted in ordinary secondary ulcer, but there is the added complication of separation and closure of the hole in the colon. In some cases this has called for a resection of the colon in addition to the manipulations necessary for the treatment of the secondary ulcer. In such a case if the treatment adopted is one of partial gastrectomy, it may involve resection and end-to-end union of the jejunum, resection of the colon, resection of the stomach and anastomosis to the intestine. This is a

truly formidable operation, and if it is not really possible to cobble up the hole in the colon, it would be better to treat the colon by means of a double-ended colostomy and so save a considerable and risky part of the operation.

Table XXVII.—SECONDARY OPERATIONS FOR GASTROCOLIC FISTULA

Separation of Viscera and Closure of Openings, with or without Formal Excision of Ulcer—	
Good	1
Fair	2
Unrelieved	1
Further operation	3
Not traced	4
Died	5
Died later	1
	17
As above, with Entero-anastomosis—	
Died 4 years later after much suffering	1
Resection of Colon and New Gastrojejunostomy—	
Unrelieved	1
Further operation	3
Died	1
	5
Separation of Fistula: Reconstitution of Normal Alimentary Passage—	
Good	6
Unrelieved	1
Further operation	1
Not traced	1
Died	4
	13
Posterior Polya Gastrectomy with Repair or Resection of Colon—	
Good	4
Not traced	2
Died	2
	8
Anterior Polya Gastrectomy and Repair of Colon—	
Requiring further operation	1
Not traced	1

In addition, 2 cases were operated on for colic fistula after posterior Polya gastrectomy. One of them was of the posterior Polya type en-Y. The anastomosis was excised and anterior Polya performed. Patient had a perforated jejunal ulcer later. In the other the edges of the anastomosis were refreshed and resutured. Later result unknown.

In these complicated cases milder operations, such as restoration of the normal alimentary passage, may well be adopted, and in the small series where this was done, almost half were cured. Whatever operative treatment is required it remains one of the most severe and trying operations in surgery.

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CHRONIC INTERSTITIAL MASTITIS

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THIS paper in entitled 'chronic interstitial mastitis' because that is the name by which the condition of the breast which it denotes is most familiarly known in this country. It is otherwise known as 'chronic cystic mastitis', 'cystic disease of the breast', 'Schimmelbusch's disease', 'Brodie's disease', 'chronic lobular mastitis', and a host of other names. A great deal of recent work on this condition, however, goes to prove that it is not of inflammatory origin and is only secondarily interstitial. The name 'chronic interstitial mastitis' should, therefore, now be abolished and a more appropriate name adopted, such as 'mastopathia', which was first suggested by Aschoff[1] and has recently been revived by Whitehouse.[2]

I am attempting to give a description of the disease and to put forward a theory of its causation which is based on the work of those who have devoted many years of research to this subject. This theory has been tested, first by the findings in an examination (which Mr. R. W. C. Murray, the Surgical Registrar, and myself have made) of the breasts of 500 consecutive female admissions to the Queen's Hospital, Birmingham; secondly, by a series of microscopical examinations of the breasts of female post-mortem cases irrespective of the cause of their death; and, lastly, by the results in the treatment of a series of cases of painful nodular breasts. In many diseases of obscure origin the trend of scientific opinion is carrying us away from the long-established idea of a focal infective causation to one which blames an imbalance of the internal secretions. The fault, it seems, of chronic illness lies not in our teeth, tonsils, or appendices, but in our glands, deficiencies in whose secretion gives rise to faults in the physiology of different organs of the body, and it is in this theory that the key to this difficult and contentious problem of breast pathology is, in my opinion, to be found.

I do not wish in this short paper to give a history of the work done on this disease, but the remarks of two early authors, Creighton and Reclus, are of importance, in that their conclusions are the same essentially as those arrived at after careful study by Cheatle and Keynes to-day.

Creighton[3] in 1878 first propounded the theory that the retained secretions in the breast were the chief factors in causation of tumours of the breast. This may be called the 'stagnation theory' and is upheld by Keynes[4] in this country and by Bertels[5] and Lukowsky[6] on the Continent. Reclus,[7] writing of the disease in 1883, called it 'intra-acinous cystic epithelioma'. He came to the conclusion that the cysts resulted from epithelial proliferation in carcinoma with degeneration of those cells and cyst formation. Cheatle's idea of cyst production, it will be seen, is a modification and elaboration of this. Cheatle[8] himself has introduced a completely new line of thought by dividing the condition into two separate varieties which he calls 'mazoplasia' and 'cystiphorous desquamative hyperplasia'

respectively, and the following is an account of these conditions based on his descriptions.

Mazoplasia is an essentially physiological process and is an epithelial hyperplasia and desquamation of the ducts and acini of the breast, mainly affecting the terminal and smaller ones. The periductal fibrous tissue increases and there is a lymphocytic infiltration of the interstitial tissues. Clinically there is said to be a diffuse aching pain over the whole of the breasts, often worse at menstruation and after excessive use of the arms. Women who suffer from this condition generally show evidence of ovarian hypofunction, their menstrual periods being of short duration and of scanty flow, and are, moreover, generally in poor health. In women with little or no subcutaneous fat, careful palpation can detect a fine state of nodularity of the anterior surface of the gland, which feels more solid than usual. This solidity may be uniform or more pronounced in one area than another. Transillumination of the breast is said to show a certain degree of opacity over the whole gland, but a trial of this method in our hands and in the hands of others whom I have consulted has proved of little or no value. This condition, according to Cheatle, is a definite separate clinical entity, and has no connection with the other variety—cystiphorous desquamative hyperplasia. Here the predominant feature is the formation of cysts, and it is said by Cheatle to have a different pathology.

Histologically, epithelial changes are seen either in the ducts alone or more commonly in the ducts and acini. In the ducts the cells become elongated, feathery, and form colostrum-like corpuscles in certain areas. Expansion of the ducts into cysts occurs. In the acini desquamation of epithelium occurs, the cells first of all becoming elongated and characteristically pale. These pale cells crowd in on the lumen, eventually disintegrate, and form small cysts, which, as the condition advances, coalesce with neighbouring cysts to form larger and larger ones. Clinically this type presents itself in three ways: first, as a single large cyst with the rest of the breast apparently normal; secondly, as a localized cystic change confined to one sector of the breast; and, lastly, as multiple small cysts scattered throughout the breasts. These, then, are the two varieties—mazoplasia and cystiphorous desquamative hyperplasia—entirely separated from each other by Cheatle.

In this paper, however, the theory is offered that mazoplasia, which is said to be a very common condition, may eventually in certain instances lead on to the cystic form of breast epithelial desquamation, and that all these breast changes are due to a faulty physiology. In other words, that all forms of non-malignant nodularity, whether cystic or not, are due to a breakdown in the hyperplasia involution cycle occurring in the breast with each intermenstrual period and leading to a physio-pathological process of excessive epithelialization and cyst formation. The thyroid is an organ which, like the breast, undergoes cyclical changes from one menstrual period to another, and it may also, owing to a faulty physiology, undergo parenchymatous changes, leading to the formation of a goitre where there is an increased formation of acini. This stage may progress by involution carried too far or not far enough to the formation of nodular areas which may show increased acinar formation or increased colloid distension. So may the breast, then, form a parenchymatous nodularity which may progress to a cystic state. The cysts which are formed may show the characters of a hypo-involution with increased epithelial lining, or of a hyper-involution where there is one single layer of flattened

epithelium. In other words, the breast may pass from the nodularity of mazoplasia to the cystic form of breast hypo-involution, and give rise, as in the thyroid, to a generalized or local cystic change or to one large cyst.

Put briefly, the theory we have to test is that mazoplasia is a common condition due to a faulty physiology which may eventually become so disordered that a further cystic change results.

It would be opportune at this point to review the normal physiology of the human breast so that it may be seen how on this thesis a perversion of that physiology may give rise to a nodularity of the breast which is at first not cystic but may eventually become so.

It has been shown conclusively that the breast responds harmonically to ovarian activity (Parkes and Bellerby,[9] Loeb and Hesselberg[10]). At puberty a definite development occurs, and during each menstrual cycle the mammary glands pass through changes characterized by hyperæmia, increase in inter-alveolar stroma, and formation of alveoli. This activity stops and the epithelium involutes in harmony with the growth of the corpus luteum. Rosenberg,[11] Polano,[12] and Dieckmann[13] have demonstrated these changes in the human breast, and Whitehouse[2] has recently pointed out that they bear a close analogy to the menstrual changes seen in the endometrium. The factor governing the hyperplastic factor of the cycle in the breast epithelial changes is the hormone produced by the Graafian follicles. Excessive epithelialization may, therefore, be due immediately either to excessive luteal activity or defective function of the rest of the ovary. As, however, there is an harmonic balance between the endocrine glands, it is possible that the remote cause may lie in the anterior pituitary, which exercises a controlling effect upon ovarian activity. In this connection it is interesting to note in passing that A. P. Thomson[14] has shown the effect of irradiation of the pituitary in relieving menstrual headaches.

Let us now trace the changes which may arise in the breast as a result of ovarian hypo-function. During the hyperplastic period of the menstrual cycle, epithelial proliferation occurs in the acini, and new alveoli are formed. In the normal breast this activity dies down and complete involution occurs. Where there is an ovarian hypo-function this involution is not complete, and a new menstrual cycle begins before the last one has, so to speak, cleared up. A further formation of epithelium occurs, the acini become packed and distended with cells, the delicate balance of secretion and absorption is upset, and fluid begins to collect in the terminal ducts and acini, giving rise to what may be called a 'precystic' distension (*Figs.* 292, 293). This condition may remain in this stage and give rise to nothing more than a persistence of the lumpiness that is more or less normal in the breast just before a period. It is not in itself painful, is a very frequent condition, and may be termed physiological.

If, however, the condition progresses, the epithelialization of the ducts and acini spreads and begins to affect the larger ducts. Moreover, as the heaped-up cells disintegrate, the acinar contents increase and distension into cysts occurs. The type of cells begins to change and the epithelium which is being formed is swollen, feathery, and stains poorly. In mazoplasia and in this cystiphorous variety a lymphocytic infiltration is seen. Lymphocytes are also seen in the thyroid in nodular states, and are probably in both organs an attempt by the tissues to counteract the mal-involution by absorption of the degenerating epithelium. Bergels[15]

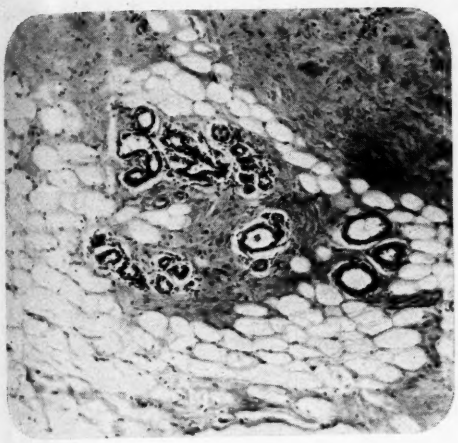

FIG. 292.

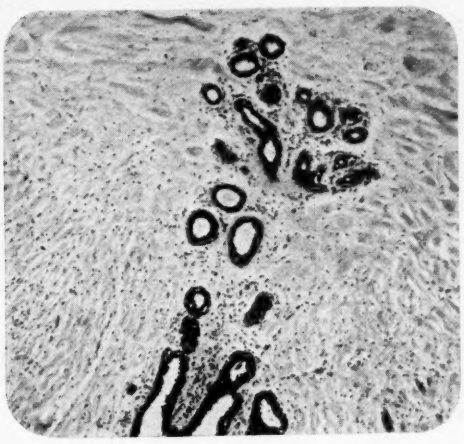

FIG. 293.

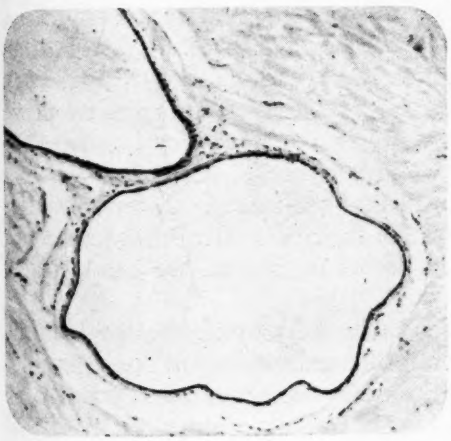

FIG. 294.

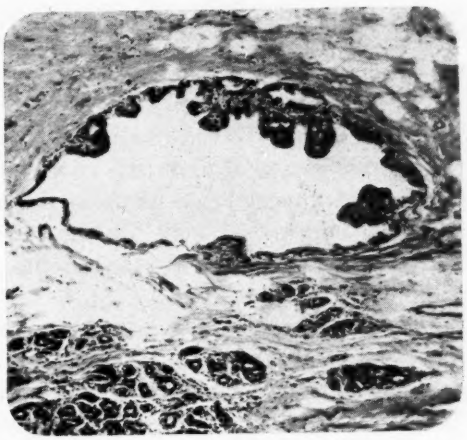

FIG. 295.

FIGS. 292, 293.—Sections of clinically normal breasts. These figures show the epithelial hyperplasia of mazoplasia. This is almost universal. The slight expansion of the ducts and acini in *Fig.* 292 has progressed in *Fig.* 293 to a precystic distension.

FIG. 294.—Hyper-involution type of cyst with a single flattened layer of epithelium.

FIG. 295.—Hypo-involution type of cyst showing papilliform projection of epithelium into the lumen (benign neoplasia).

FIG. 296.—The same type of case as *Fig.* 295, but showing at A the epithelial outgrowth becoming sessile and the disappearance of the connective-tissue element (pre-malignant).

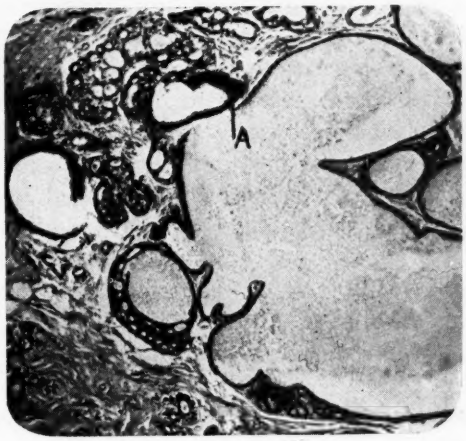

FIG 296.

states that they are always present where a physiological or pathological autolysis is in progress.

There are two schools of thought with regard to cyst formation: one, which blames obstruction by plugs of epithelial débris, inflammatory processes, and proliferating connective tissue, and the other which regards them as due primarily to an epithelial hyperplasia. Cheatle, who holds the latter view, points out that the strong-walled ducts alone may undergo cystic change, while the delicately-walled acini in communication with them are unaffected; whereas the reverse would occur were obstruction the cause. Moreover, where scars or large carcinomata affect the base of the nipple and mechanically obstruct all the ducts there is often a complete absence of dilatation of their peripheral branches and acini. Of the women in our series, 15 had had breast abscesses opened years before, but of these only 2 showed any nodularity whatever, and even these were not demonstrably cystic, in spite of the scarring and subsequent duct obstruction which must have occurred.

It is held in this article that all cysts are due to faulty involution; frequently they are found to have the appearance of a true retention cyst, the lining consisting of one flattened layer of cells with no evidence of cellular proliferation anywhere. These are to be regarded as areas of hyper-involution (*Fig.* 294). Cysts with an epithelial lining are the result of an incomplete involution (*Figs.* 292, 293, 295). The next stage from cystic formation is the supervention of epithelial neoplasia which may occur in the more active parts—that is, in the smaller cysts, where the epithelium is not degenerated so extensively. This epithelial neoplasia is at first benign and appears as a papilliferous outgrowth into the lumen. Later still these epithelial outgrowths may become sessile and lose their connective-tissue element; the cells are de-differentiated and the picture begins to take on the characters of malignancy (*Fig.* 296).

It does not follow that this change will occur in every cystic breast; it is the supervention of a different process—that of epithelial neoplasia upon one of epithelial desquamation—whether *post hoc* or *propter hoc* only further research can decide. The facts that the fluid in cysts contains irritant substances such as urea, that experimental tar carcinomata of the breast in rodents show the stages of preliminary desquamation, and that there is evidence that cellular growth is stimulated by autolysis of cells apart from any irritant substances produced by such autolysis (Drew[16]), are reasons for believing that cystic changes in the breast may lead in certain cases to malignancy.

Cheatle states that 20 per cent of all carcinomata originate in cystiphorous desquamative hyperplasia. Five cases of the women examined by us had had cysts removed locally at times varying from two to ten years previously. Four of these had completely normal breasts, the remaining one was in hospital for removal of a cyst which had developed in another portion of the same breast.

THE INVESTIGATION

The 500 cases which formed the material for our investigation ranged from the ages of 10 to 80 and were divided into age groups of 10–20, 20–30, 30–40, 40–50, and 50 upwards. Nodularity of the breast in greater or less degree, and showing all the clinical signs indicative of mazoplasia, was found in 144 cases—a

percentage of 28·8. Of these 144 cases, 66 were single and 78 married. (Of the latter 78, 40 had suckled one or more of their children.) The pecentage incidence of nodularity in the various groups was as follows:—

10–20	..	..	28·6
20–30	..	..	33·0
30–40	..	..	32·0
40–50	..	..	33·0
50 upwards		..	21·0

These figures show in a striking manner the universality of the nodular breast (*Fig.* 297). It is, roughly speaking, equally common in the married and unmarried, and the three decades between 20 and 50 show a remarkable equality in the incidence of the condition—namely, 33, 32, and 33 per cent.

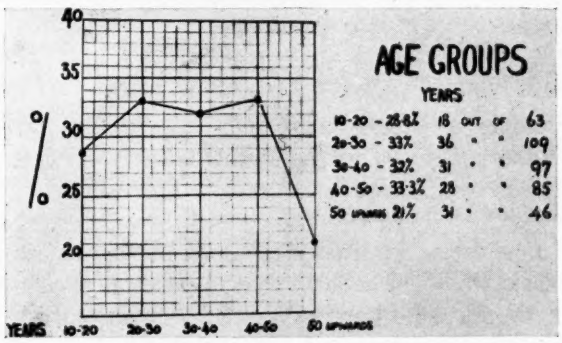

FIG. 297.—Graph showing incidence of nodularity in various age-periods.

Nearly all of those who were between puberty and the menopause showed signs of ovarian hypofunction, their periods being painful and scanty, and were of the asthenic, chronically unhealthy type. Before puberty it does not occur, and after the menopause an involutionary cure is brought about. Brodie,[17] in his original description of the disease in 1846, says: "To complete the history of the disease as it first shows itself I may add that the general health is unaffected, that the patient complains of no pain unless it be that in some instances there are disagreeable sensations that are apt to arise wherever the attention is anxiously directed to any one part of the body." The truth of this statement was borne out by the fact that of the 500 cases examined, only 46 complained of pain in the breast, and that of these 46, 20 (nearly half) had no signs of mazoplasia or cystic change whatever. Moreover, in the 26 who had nodular breasts which *were* painful, it was found that the pain bore no relation to the degree of nodularity found.

By far the majority of nodular breasts—98 out of 144 (68 per cent) made no complaint whatever of pain, and the conclusion became obvious that pain was not a feature of the condition, but was, as Brodie suggested, "a disagreeable nervous sensation arising when the attention was anxiously drawn to that part"; and I cannot help feeling that in the past many breasts have been removed not so much on the clinical findings and judgement of the surgeon as on the demands and anxiety of the patient.

That the definitely cystiphorous stage is relatively uncommon was shown by the fact that only 20 out of the 500 had demonstrable cysts in their breasts. I have no doubt, however, in view of the pathological findings, which I refer to later, that in many of the 144 cases of nodular breasts small clinically unrecognizable cysts would have been found if the affected portions had been excised and sectioned.

There were 33 cases of carcinoma of the breast in the series: of these, 6 showed nodularity or cystic change elsewhere in one or other breast, giving a percentage of 18, which is a figure approximately the same as that given by Cheatle for carcinomata arising in cystic breasts. It is of course possible, however, that the nodularity in these cases was secondary to the malignant growth.

The average age of patients with non-cystic nodular breasts was 36, in those with cysts it was 40, and in the malignant cases 50.

PATHOLOGY

A series of sections of breasts of female post-mortem cases with no history of breast disease were provided by the Pathological Department of the Queen's Hospital, Birmingham, and were examined. The following conclusions were arrived at:—

1. **Mazoplasia.**—It was expected in view of the clinical frequency of nodular breasts that mazoplasia would be seen in a large percentage of these sections. The histological picture of the condition was actually found in almost every instance (15 out of 17) whether cysts were also present or not.

2. **Cysts.**—If mazoplasia, a very common condition, is the first stage of a process leading to clinically obvious cyst formation, as is held in this paper, then an intermediate stage where cysts are demonstrable microscopically only should be found with a frequency less than that of mazoplasia but greater than that of clinical cystic disease, and this in effect was what these sections showed. Out of 18, 8 showed cysts larger than that of the average glomerulus. Moreover, in these sections there were always to be found areas of mazoplasia, and all stages of cyst formation from the slight terminal distension of ducts and acini seen in the latter, to those visible to the naked eye, and showing all the characteristic cytology of cystiphorous desquamative hyperplasia. In short, the difference between mazoplasia and the cystic breast seemed to be in degree and not in kind.

Histologically some cysts are true retention cysts with no evidence of epithelial hyperplasia. These are to be explained as a localized area of hyper-involution. In two cases papilliform projections into cysts were seen. These epithelial proliferations were hyperplastic and not neoplastic, the cells being equal and typical.

A series of sections of portions of cystic breasts removed surgically were examined, and in some cases (*see Fig.* 296) the benign neoplasia seen in the walls of cysts where cellular activity was greatest showed a different picture. The connective-tissue element of the papillæ had decreased, and cell masses were formed. The cells were not irregular and atypical, but the possibility of such a condition being precancerous cannot be ignored; the post-mortem cases, however, show

that unsuspected cysts are so frequent that the cystic state cannot be generally condemned. Cases should be treated as premalignant only when microscopical section following biopsy reveals the picture just described.

TREATMENT

To test the clinical application of the theory of the endocrine causation of painful nodular breasts a small number of cases treated by Mr. Hugh Donovan as out-patients were followed up, and with his permission are included in this paper. To these were added a few patients seen in the Casualty Department and treated there. In all they numbered 15, and the treatment was by the administration of ovarian residue for the last half of the intermenstrual period. In Mr. Donovan's cases the procedure employed was that advised by Cheatle and Cutler—namely, to order the patient to take tablets of ovarian residue containing 5 gr. three times a day. The tablets used were those made by Paynes & Burn. Recently, however, all patients have been treated with daily injections of the Parke Davis product known as Theelin, recommended by Professor Whitehouse, during the same period of time: 2 c.c., corresponding to 100 standardized Doisy Rat Units, were given at each injection. Twelve of these patients, of whom 5 had definite cysts, reported a remarkable improvement as regards pain, and there was a noticeable dimunition of nodularity. In 3 cases all traces of knottiness had disappeared. In the remaining 3 there was no improvement.

No direct control such as the injection of sterile water was employed in this series, but 9 of the patients had previously had courses of X-ray treatment without any benefit, clinically or symptomatically, being reported by any of them. This small series of cases in conjunction with the series published by Cutler and Whitehouse show that treatment by the œstrus-producing ovarian hormone has a definite place in the treatment of this perversion of breast physiology. It cannot, however, be expected to replace surgery where there is a gross cystic change. The treatment by puncture, aspiration of cysts, and subsequent ovarian therapy mentioned by Whitehouse must have a limited application.

CONCLUSIONS

1. Non-cystic nodularity of the breast is a very common condition and is due to a faulty physiology dependent upon endocrine disorder.

2. This non-cystic nodularity may in certain instances pass on to a cystic state and is always a precursor of such cystic state, and this condition of the breast in all its stages should be known by one name as 'mastopathia', first suggested by Aschoff and recently adopted by Whitehouse.

3. The condition commonly is not painful.

4. Unless cysts are obvious, treatment should be by ovarian residue aided by attention to the general health of the patient. In cystic states, local removal should be performed and further treatment decided by careful pathological examination; only a definitely malignant picture should call for a further radical operation.

Pre-malignant cases should be treated by a local amputation of the affected breast.

My thanks are due to the Honorary Surgical Staff of the Queen's Hospital, Birmingham, and to Mr. Hugh Donovan especially for their advice and kindness in providing me with the material for the investigation which was carried out for the purpose of this paper.

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INTERSTITIAL RADIUM TREATMENT OF CARCINOMA OF THE BREAST: DESCRIPTION OF A RADICAL TECHNIQUE

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THE radium treatment of mammary carcinoma presents many diverse problems, as the method of treatment must take account not only of pathological anatomy, but also of the laws which govern the activity of the therapeutic agent. No uniformity of technique has yet been achieved by those who practise this branch of therapy. Various combinations of surface and interstitial methods have been, and are being, tried. The whole tendency in modern radium practice is away from interstitial methods towards external radiation. Unfortunately, mammary carcinoma does not lend itself to surface radiation by radium to any satisfactory extent. Short of telecurietherapy, it is not practicable to deliver a high dose throughout the potentially affected tissues, including the complete axilla and the internal mammary zone. In the present state of our knowledge, therefore, we must rely basically on interstitial methods. Nevertheless, it is probable that the ultimate choice in radiation therapy will be a combination of deep X rays and interstitial radium therapy, and already Pfahler, Kaplan, and others have formed favourable impressions of this procedure. Maximum efficiency of such a technique depends, however, upon the thorough exploration of these methods individually, so that an accurate assessment of the limiting possibilities of each may be made. The present communication deals entirely with the interstitial aspect of this problem.

Many interstitial techniques have been evolved. In this country and in America that published by Keynes has become almost standardized, and it is too well known to any who are interested in this subject to require description here. The method is open to criticism, as are all others to-day, but it has justified itself by the results achieved. These cannot be questioned, and some of Keynes's latest figures are convincing evidence that this method must hold a definite place in the treatment of cancer of the breast.

Kaplan has employed a modification of Keynes's technique which does not, however, appear to improve upon the original. Perhaps his most notable modification is the use in some cases of very long needles—up to 9 cm., with filtration equivalent to 0·5 mm. Pt—inserted in relation to the breast and into the axilla. A similar modification is employed by Cutler, and by Lamont and Morrison in Glasgow. Souttar, Kaplan, and Lee and Pack have employed gold seed implantation as a method. Failla and Lee and Pack use capillary gold tubing containing emanation, cut to suitable lengths. Meland's technique resembles closely that of Keynes, and Monchaux uses a similar distribution except in relation to the breast itself, where he employs two concentric circles of needles. Various other modifications of Keynes's technique, and combination of it with X rays or surgery, or both, are in use.

Several criticisms are levelled at the interstitial method. Murdoch and Simon,

admitting that needling is capable of delivering a greater amount of actual energy to the tissues than can be delivered by surface methods, nevertheless condemn the procedure on the grounds of impossibility of attaining homogeneity. Such criticisms miss the fact that what is required is not homogeneity—admittedly impossible—but attainment throughout the whole area of a minimum intensity which will be lethal for the tumour cells, with a maximum intensity which will be insufficient to interfere with the vitality of the normal tissues.

Regaud admits that needling is a simple and efficacious way of dealing with the primary growth in the breast, but has given it up for the fundamental reason that he believes it to be dangerous as being productive of metastases. Such a statement demands attention, but would appear to lack actual proof. Lee, Pack, Quimby, and Stewart state that in a series of 130 cases treated by interstitial methods they have not seen evidence of dissemination from this cause.

One of the major difficulties is to secure a satisfactory distribution of radium foci. This article describes a technique which is designed to surmount this obstacle. Theoretically it is hardly possible to contradict Souttar's claim that gold seeds are the nearest approach to the ideal vehicles for attaining relative uniformity of radiation. Lee and Pack, however, deal with this matter in an interesting article on measured tissue dosage in the radiation of mammary carcinoma. With reference to the relative claims of gold seeds and of linear foci they have shown in their experience that the practical difficulties of distribution of gold seeds outweigh theoretical considerations, and have adduced not only radiographic but also histological evidence in favour of their contention. Cutler and Martin discuss this question also, and decide in favour of needles. Irradiation by linear foci would, therefore, appear to be the method of choice for interstitial work.

All the interstitial methods published to date are incomplete. In 1931 Birkett criticized Keynes's method on this ground, admitting, however, that the final issue could lie only with the results. As mentioned above, Keynes's recent publications have supplied a satisfactory answer up to a point. Satisfactory results *have* been obtained, but it is a question of improving upon them. If methods admittedly amenable to improvement are capable of giving useful results, better results may be expected from a successful revision of the methods. Where Keynes's technique falls short, the other techniques are equally faulty. All are subject to criticism on two main grounds: (1) Incompleteness of radiation as regards the upper axilla, supraclavicular area, and internal mammary zone; and (2) The faulty physical conception of the distribution of radium foci.

In spite of these criticisms, Keynes with his standard method was able in 1929 to show initial good results in 67 per cent of cases in Grades I and II and in 46 per cent of cases in Grade III, with 30 per cent of apparent cures taking all groups together. At the Meeting of the British Medical Association (Dublin, 1933) he stated that 7 out of 25 (28 per cent) inoperable cases treated had survived for five years without disease.

Souttar's experience has been such as to convince him that the surgeon can offer radium implantation as an alternative to surgery without fear of prejudice to the interests of the patient.

Lee and Pack consider that interstitial implantation can be safely advised when operation is contra-indicated, and that it is justifiable to employ the method in primary operable cases.

RADICAL TECHNIQUE

In comparing radiological with surgical history, it is relevant to note two points: (1) The striking improvement in surgical results ushered in with the introduction of the radical (i.e., surgically complete) technique in amputation; and (2) The strikingly poor results in cases treated by operations of the incomplete type, as shown in such publications as those of Greenough and Lane-Claypon. If the radiological parallel could be achieved, it is felt that results would improve in a manner equally impressive. Using Keynes's technique as a starting-point, work has been going on in the Holt Radium Institute, Manchester, for the last two years or so, in the gradual evolution of a technique which is now brought forward with the claim that it is a radical (i.e., radiologically complete) implantation. It is introduced as being surgically and radiologically sound, and as having been tested thoroughly as to practicability over a considerable number of cases to date.

The modifications of existing methods involved differences in dosage, in volume-irradiation, and in anatomical considerations so essential as to bring the method within the confines of the experimental. The technique has therefore been developed on inoperable cases, mostly well beyond the bounds of the most optimistic surgery, many beyond the bounds of reasonable radiological expectation. In view of practical experience of the method, however, and of the good results obtained by other implantation methods, it is felt that its application now to operable cases in certain circumstances is entirely justified, and that it must be considered seriously in those cases of border-line operability in which the results of surgery alone are so disappointing. It is not, however, pressed at present as a method of choice to be used to replace surgery with its known results.

The technique as developed in Manchester is as follows:—

1. **Breast.**—According to the size of the breast (tumour *qua* tumour is disregarded) one or more layers of needles are inserted from medial and lateral sides, in such a way that the needles of the deepest layer, undercutting the breast, do not meet in the centre, and that any subsequent more superficial layers approximate gradually more closely until the effect achieved is that of a cone of radio-active foci with a central zone adequately irradiated but not containing actual needles. The peripheral ends of the needles are crossed at the base of the cone, and occasionally in the subareolar area one or more needles are inserted at 90° to the deeper planes to close the apex of the cone (*Fig.* 298). Such peripheralization of radium foci avoids the high central intensity, falling rapidly towards the periphery, inevitable when any volume of tissue is implanted in a uniform or in a cart-wheel manner. The needles used are of a content of 3 mgrm., active length 4·5 cm. screened by 0·5 mm. Pt, and of 2 mgrm., active length 3 cm., with similar filtration.

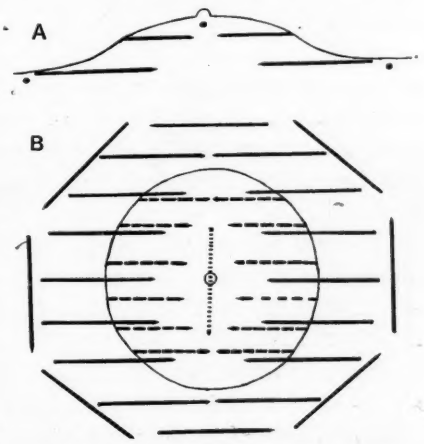

FIG. 298.—Diagrammatic representation of breast implantation in three planes. A, Elevation; B, Plan. Deepest layer of needles continuous: other layers dotted.

2. **Axilla.**—For purposes of radiation the axilla is divided into two separate areas—base and apex. As in the case of the breast, peripheralization of the radium foci is aimed at.

a. Base.—Depending upon the patient's build, a variable number of needles, usually two, three, or four, is inserted along each of the four walls of the axilla. The medial ones run in close relationship to the chest wall; the lateral in close relationship to the great vessels; the anterior in the interpectoral plane; and the posterior in relation to the anterior surface of the subscapular muscle. The general effect is that of a cylinder of needles, as shown in *Fig.* 299. All these needles are of 3-mgrm. content with active length of 4·5 cm. and with 0·5 mm. Pt filtration.

b. Apex.—Two or more needles are inserted parallel to the clavicle, running deeply in the pectoralis major close to the costocoracoid membrane. Two or more of the same type are inserted through the pectoral musculature at 90° to the chest wall at the level of the upper axilla, forming tangents to the ribs, the upper one calculated to pass just below the line of the vessels. These two sets of needles form a bracket round the antero-lateral aspect of the upper axilla. To complete

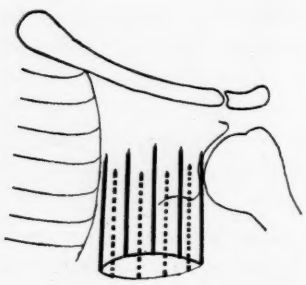

FIG. 299.—Diagrammatic representation of implantation of base of axilla, showing cylindrical effect.

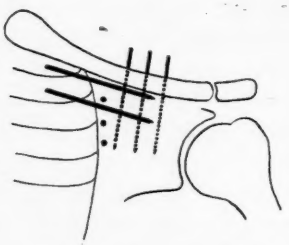

FIG. 300.—Diagrammatic representation of implantation of apex of axilla. Retroclavicular needles dotted.

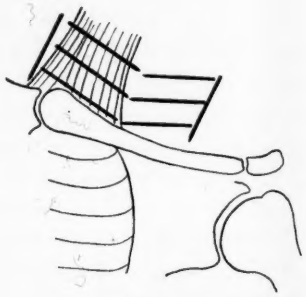

FIG. 301.—Diagrammatic representation of implantation of supraclavicular area.

the bracketing of the upper axilla, two or three needles are inserted from above the clavicle, and run down into the apex of the axilla. The most medial needle is inserted immediately lateral to the third part of the subclavian artery. Anatomical necessity determines that these needles run along the postero-lateral aspect of the apex of the axilla. All the needles are of 3-mgrm. content, 4·5 cm. in active length, and filtered with 0·5 mm. Pt. X-ray photographs demonstrate that a satisfactory distribution of these needles can be achieved. Up to the time of writing no damage to important vessels or other structures has occurred. The distribution in indicated in *Fig.* 300.

3. **Supraclavicular Area.**—Three needles are inserted deeply into the substance of the sternomastoid muscle, directed lateralwards from its medial border. Three others are inserted in the opposite direction, running across the posterior triangle to meet, or almost meet, the points of the former. A vertical needle is inserted at the level of the heads of each of these sets of needles in order to increase the field of irradiation to a satisfactory extent. In this way the two sets of needles are made to form a bracket round the lower part of the great vessels at the root of the neck. Several of the X-ray photographs demonstrate this, and *Fig.* 301

illustrates the technique. The needles used in this field are of 1·33-mgrm. content, of 2 cm. active length, and are filtered with 0·5 mm. Pt.

4. **Mediastinum.**—Using any suitable seed-introducer, such as Souttar's gun, three gold seeds are inserted into the anterior mediastinum through each of the upper four intercostal spaces. Usually seeds of 1·5 mc. strength and screened with 0·5 mm. gold are used. The cannula is inserted obliquely into the intercostal space until the edge of the sternum is encountered. From that as starting-point it is introduced under the edge of the sternum and under the edge of each of the adjacent ribs in turn, one seed being deposited at each of these points, so that there is a triangle of seeds in the mediastinal area opposite each of the upper four intercostal spaces. *Fig.* 302, prepared by Mr. H. M. Parker, Physicist to the Institute, indicates the field of intensity round such a distribution of gold seeds as opposed to that round a single needle of 1·33 mgrm. and 2 cm. active length.

FIG. 302.—Mediastinal technique. A, Three gold seeds, 1·5 cm. apart, each = 1·5 mc.; filtration = 0·5 Au. Time = ∞. Area receiving 6000 'r' units or more is shaded. B, One 1·33-mgrm. needle, active length 2 cm.; filtration = 0·5 Pt. Time = 7 days. Area receiving 6000 'r' units or more is shaded (same scale as A). (*By Mr. H. M. Parker.*)

The advantage of the former over the latter is apparent, and becomes even more obvious when it is considered that the seeds lie in the plane of the mediastinum, whereas a considerable part of the active length of any mediastinal needle must always be superficial to this plane. Indeed, in obese patients the slant of the mediastinal needle becomes of necessity very considerable, and its insertion at all a matter, in some cases, of extreme difficulty. Where no gold seeds are available, however, needling is employed as described by Keynes, but using when possible two needles in each interspace instead of one.

FEATURES OF THE NEW TECHNIQUE

It will be noted that the main features of the technique as described are:—

1. The radiation of a large volume of tissue in continuity. In so far as such a feature can be illustrated, this is seen in some of the X-ray photographs.

2. The application of the allied principles of peripheralization of radium foci and of cross-fire radiation. These features also are illustrated to some extent in certain of the accompanying X-rays.

3. The new approach to the problem of mediastinal lymphatic area involvement.

4. The new approach to the radiation of the upper axilla so that an unbroken volume of radiation extends from breast to supraclavicular area.

5. The extended radiation of the supraclavicular zone.

Stereoscopic X-ray films bear out the contention that it is possible to radiate the breast and its lymphatic areas in a satisfactory manner. Already the study

of such films has led to a number of modifications and improvements, and so valuable has been the information thus secured that any new departure in technique is now critically examined by this means. This method of examination cannot be too strongly recommended to any who may consider the adoption of a technique such as has been described.

While non-stereoscopic films are somewhat confusing, and at times a little difficult of interpretation, they afford, nevertheless, some indication of the various features described above. A number of these are reproduced herewith, and serve to illustrate the gradual development of the technique described, as well as its more distinctive features. *Fig.* 303 shows an early phase, roughly corresponding to the

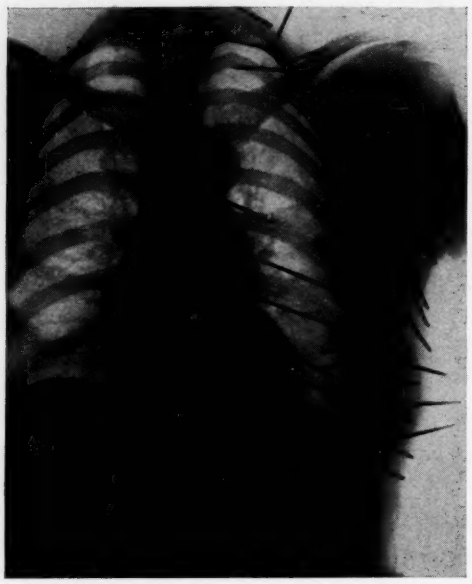

FIG. 303.—X-ray illustrating development of radical technique. Early stage. Conforms roughly to Keynes's technique, but with omission of infraclavicular needles.

FIG. 304.—X-ray illustrating development of radical technique. Later stage. Note: (1) Two antero-posterior needles in upper axilla; (2), Two infraclavicular needles; (3) 'Hollow cone' implantation of breast.

Keynes technique, but with omission of infraclavicular needles. The presence of these last would have improved the radiographic effect, but would have done little to radiate the upper axilla. This problem of the upper axilla called for serious consideration, and *Fig.* 304 shows an early attempt at its solution. Satisfaction was experienced, however, only with the introduction at a later date of retroclavicular needles, as shown in *Figs.* 305 and 306 and also in subsequent prints. Minor modifications in supraclavicular and mammary distribution followed, and can be seen in *Figs.* 306 and 308. At this stage it was felt that a sufficient volume was being radiated in continuity, but that the radiation of the internal mammary zone—by needles inserted in the intercostal spaces—was inadequate. The final step in the evolution of the technique was devised to meet this criticism, and is illustrated in *Figs.* 307 and 308, where three radon seeds have been inserted via each of the upper four intercostal spaces, and are lying in a plane posterior to the deep aspect of the sternocostal junctions.

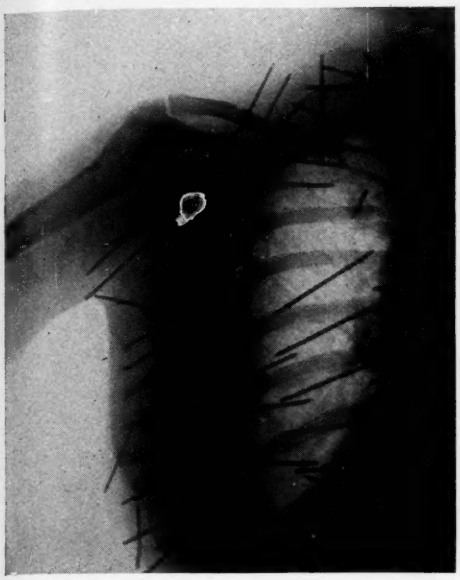

FIG. 305.—X-ray illustrating development of radical technique. Later stage showing: (1) Supraclavicular bracket region of great vessels; (2) Complete axillary implant, with retroclavicular needles.

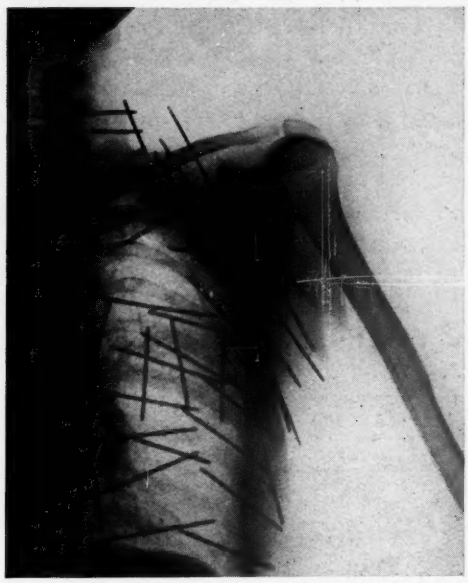

FIG. 306.—X-ray illustrating development of radical technique. Later stage showing: (1) Supraclavicular bracket; (2) Continuous axillary irradiation; (3) Peripheral outlining of breast field; (4) Duplication of intercostal needles.

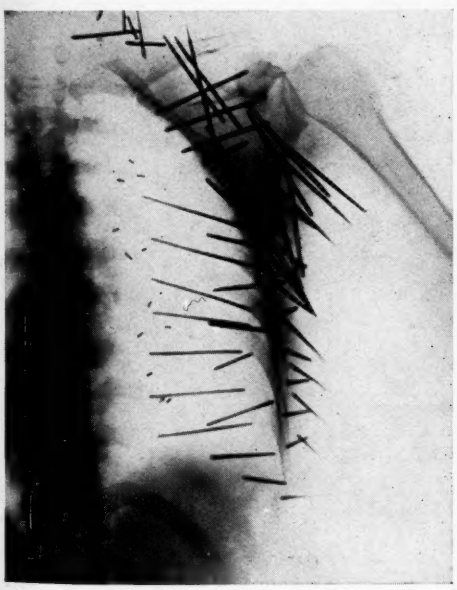

FIG. 307.—X-ray illustrating development of radical technique. Later stage showing previous features and illustrating the gold seed technique for the internal mammary zone. One of the antero-posterior needles of the upper axillary group can be seen end-on.

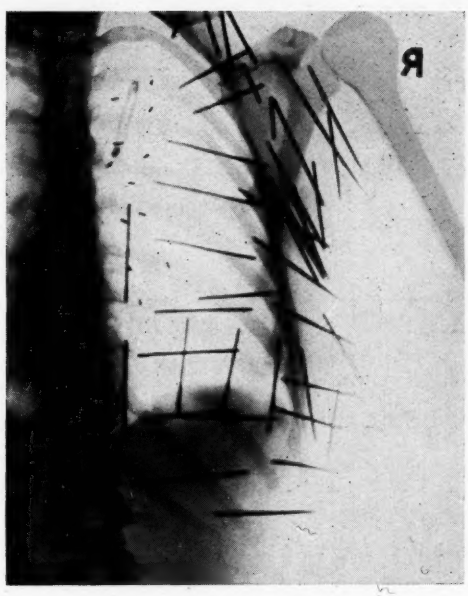

FIG. 308.—Illustrating development of radical technique. Similar to *Fig.* 307, but with peripheral outlining of breast field.

DURATION OF TREATMENT, END-RESULTS, ETC.

Duration of Treatment, etc.—The needles are left in position for seven days as a rule, but this period has been empirically arrived at, and there is room for experimental determination of the optimum time-factor. Alteration of the time-factor could, of course, be carried out, if desired, without modification of the total dose, as the total number of needles could be increased or diminished, or the linear intensity modified, without departure from the distribution outlined above.

During treatment the arm on the affected side is kept at rest with the humerus abducted to a right angle. The object of this is to prevent undue reaction on the skin of the axilla by maintaining the disposition of the axillary needles. Pillows are not satisfactory for this purpose, and a suitable splint is worn. The reaction usually proceeds to the extent of a mild radio-epidermitis in one or more areas.

Definite blood changes are produced as the result of the radiation of such a volume of tissue. A sharp fall in the white-cell count is an invariable accompaniment of the treatment. Dr. Goodfellow, who has been working on this problem for some time, informs me that an immediate leucocytosis—in most cases confined to the polymorphonuclear cells—is followed by a steady fall in the number of white cells, most notable in the case of the lymphocytes.

End-results.—As experience of distribution of radium foci and of total dosage accumulates, complete disappearance, not only of the tumour mass, but also of glandular deposits, becomes more and more frequent. Indeed, it can be stated that there appears to be an optimum dosage at which even the largest primary and secondary masses, provided that the tumours are of sensitive type, undergo complete resolution, leaving no trace of their presence. When such dosage is not achieved, residual indurations, sometimes very vague and indefinite, sometimes more localized, may occur. It seems from the consideration of cases in one's own experience that such residues can occur as the result of departure from the optimum dosage in the direction either of insufficiency or of excess. That some workers have demonstrated in such masses cancer cells in apparently vital condition is no proof that the same would hold after more appropriate amounts of radiation. It must be the experience of all radium workers that high dosage in any tissue is liable to produce definite induration. Such an effect is probably peculiarly liable to occur in the breast, the areolar tissues of which appear to lend themselves readily to some form of proliferative fibrosis under radiation.

The complete and striking disappearance of affected lymph-glands in many cases is interesting, and disappearance of these seems to be more consistently achieved than of the primary growth itself.

The work described in this article was initiated in the latter half of 1931. For reasons previously stated the treatment was confined to very advanced cases, except in occasional instances when other factors, such as the general condition of the patient, had to be taken into account.

In the course of 1931 and 1932, 53 cases were treated, starting on the model of Keynes's technique and gradually evolving therefrom. During this period the policy was consistently adopted of referring all apparently operable cases for surgery, and of treating earlier cases only if there were definite surgical contra-indications. Of the 53 cases treated, 17 (32·1 per cent) are alive over one year

and under two years. Such a figure is gratifying in consideration of the material used. With the exception of 5 cases, all belonged to the late, inoperable group. Of the 5 earlier cases, 3 are alive, and one of the dead was an old lady of 73 years who died during sleep on the sixth day after treatment on account of cardiac failure. If this case is excluded for the purpose of assessing the effects of radiation, we are left with 75 per cent in this group—admittedly so small as to be of little consequence.

The radical technique, as described, may be regarded as having been in operation throughout 1933 only. It is therefore not possible to speak of its results from a statistical standpoint. The immediate results, however, are encouraging, and, as experience accumulates, the proportion of cases in which disappearance of the primary growth and of its secondaries takes place without leaving any palpable residue is definitely increasing. Up till October, 1933, the method was employed in 23 cases in which sufficient time has elapsed to enable the immediate result to be assessed. Of these 23, 14 are alive and well, 6 are alive with evidence of disease, which may yet be amenable to further treatment, and 3 are dead. Of the 23 cases 20 belong to the late, inoperable group; of the 3 earlier cases, 2 are alive and well without palpable trace of their malignancy.

Such results are not conclusive, but it is felt that there is reason for a measure of optimism. Much work remains to be done in this and in other fields before the last word can be spoken on the treatment of mammary cancer. In the meantime each case presents its own individual problem.

SUMMARY

1. Although the results of interstitial radium therapy as practised by Keynes have established this form of treatment as a method of real value, current techniques are amenable to improvement.

2. The technique described in this article is sound in principle, safe in practice, and is claimed to be a radical radium implantation.

3. There is an optimum dose with which complete resolution of primary and secondaries can be achieved.

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DIAPHRAGMATIC HERNIA

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(*Being an Arris and Gale Lecture, delivered at the Royal College of Surgeons of England on February 23, 1934*)

ALTHOUGH instances of diaphragmatic hernia not due to trauma have long been recognized, the condition is still sufficiently rare, of sufficient gravity, and there remain so many debatable questions associated with it, to make it desirable that the investigations carried out in a series of cases should be recorded.

Sir Arthur Keith[1] and Basil Hume[2] have written on the embryology, and Woodburn Morison[3] has reviewed the history and discussed the radiology of the subject. A. F. Hurst[4] and his colleagues have published most valuable clinical records. The late R. P. Rowlands, Salisbury, Lake, and others, have each published a case operated upon with cure of the patient. The total number of published cases operated upon in this country would appear to be small; while in America C. A. Hedblom[5] had published as long ago as 1925 a series of 9 cases operated upon by him, and Stuart Harrington[6] a series—including 13 of traumatic origin—of 45 cases from the Mayo Clinic in 1931. It can scarcely be that the proportion of cases in the population should be so much higher in America. We must rather believe that, in patients with doubtful symptoms, the search is more thorough in the big American clinics, and that when a diaphragmatic hernia is found to be the cause of disability the patient is more frequently offered, or asks for, surgical relief.

A number of cases in infants have been reported in British journals. Formerly most of these were discovered post mortem, after a short and distressing struggle for life had ended. The death-rate in infancy is high because the extent of the defect in the diaphragm is in some cases so extensive that it is scarcely compatible with life. This aspect of the question has been admirably dealt with by N. R. Barrett and C. E. W. Wheaton.[7] When the defect is not such as to terminate life in infancy the individual may lead a normal life until a later period, when symptoms may appear more or less gradually. The patients upon whom the investigations set out in this paper have been made have come under my observation at this later period of life.

As the literature of the subject has been frequently and recently reviewed and is readily accessible, it would seem to be most useful to give my personal experiences.

My series is made up of 25 patients in 11 of whom the œsophagus was of normal length, with part, or the whole, of one or more abdominal organs herniated into the thorax. In the remaining 14 patients the œsophagus was congenitally short and a portion of the stomach was situated in the thorax. Of the former 11, 8 were carefully investigated clinically and radiologically and then operated upon. The latter 14 patients—with short œsophagus—were investigated on the whole less completely because in most of these cases the investigations were not completed

by operation. Apart from the relief given to the patient, operation has afforded the opportunity of confirming diagnosis and verifying the anatomical conditions present. The " pathology of the living " will always remain of interest and value, for the patients are alive and available for subsequent observation. Even though patients with a short œsophagus may not in the majority of instances, or in the present state of our technical skill, be so suitable for operation, observation of some of these patients over a period of years has given valuable information, so that we become more familiar with the behaviour and prognosis of this by no means rare condition.

CLASSIFICATION

A number of classifications have been published. Perhaps the time has scarcely arrived for one which would be universally acceptable. If each investigator arranges his cases in the manner that best illustrates his findings, a suitable classification will emerge. For these reasons I have arranged my cases according to the site at which the abdominal organ, or organs, entered the thorax. As none of these herniæ has followed any known injury, I have assumed that they are congenital. Seeing that imperfections of development are so well recognized in other parts of the body, constituting such deformities as hare-lip, cleft palate, spina bifida, imperforate anus, and hypospadias, it would be strange if a structure so complicated in its origin as the diaphragm did not sometimes fail to develop perfectly, and, furthermore, if fusion is less than perfect, the strains to which the diaphragm is subjected in early life (for example, during the spasms of infantile crying) are likely to make manifest any frailty. While it cannot be denied that some of these herniæ may have been acquired during life—muscle fibres torn in the spasms of whooping-cough with hæmorrhage followed by fibrosis and stretching—embryological evidence obvious by skiagraphy or revealed at operation shows that some at least are congenital.

The sites of the hernial orifices in the diaphragm in my series are as follows :—

	Cases
I. Retrosternal (synonyms—Parasternal; Foramen of Morgagni) ..	1
II. Left dome	2
III. Costo-vertebral region—left (synonym—Hiatus pleuro-peritonealis). (?) Non-development of left crus	3
IV. Œsophageal region—	
1. Hernia diaphragmatica transversa. The œsophagus is of normal length; the anatomical hiatus is replaced by large defect.(?) Due to non-development of crura	3
2. Para-œsophageal. The œsophagus is of normal length; the hiatus is anatomically normal but dilated	2
3. Short œsophagus, with partial or complete thoracic stomach ..	14

The description of the clinical types will be more readily understood if the development is considered. I am indebted to my colleague, Dr. Woollard, Professor of Anatomy, St. Bartholomew's Hospital, for the notes on embryology, and to his department for the drawings illustrating them.

DEVELOPMENT OF THE DIAPHRAGM

From our point of view there are three stages. In the first the cœlomic space is continuous, until the growth of the embryonic organs subdivides it into pericardial cavity, pleural space, and peritoneal cavity. The pericardial cavity lies ventrally, is immediately in front of the septum transversum, and communicates

dorsally and in front (cranially) with the enlarging pleural space. The pleural space joins over the dorsal margin of the septum transversum with the peritoneal cavity. The channel of communication is called the pleuro-peritoneal canal (*Fig.* 309). and the walls of the canal are the pleuro-peritoneal membranes. The septum transversum (*Fig.* 310) is restricted to the ventral half of the embryo. The interval left between its dorsal margin and the back of the embryo is occupied by the canals just mentioned, by the developing œsophagus, and by stomach suspended in the median plane by the mesentery, and for a time by the growing lungs.

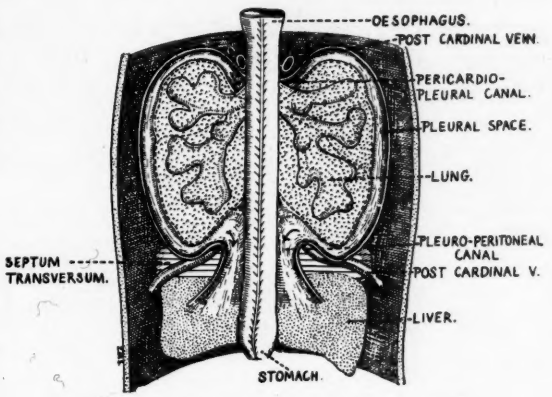

FIG. 309.—Showing pleuro-peritoneal canal.

It is clear that if the pleuro-peritoneal canals should remain open through deficiency in the growth energy of the parts whose proliferation normally closes them, then the pleural and peritoneal cavities will not be separated completely from one another, and the positive intra-abdominal pressure sooner or later will carry some or other of the abdominal organs into the thorax. This is one of the commonest types of hernia in infants, but if it occurs at this stage no sac is present, for the pleuro-peritoneal canal has not been closed. In the great majority of infants who die as the result of a diaphragmatic hernia in the first few hours or days following birth, and in whom no sac is present, the hernia has probably occurred at this stage. This fact has given rise to the statement by Keith, Hume, and others that in herniæ in the pleuro-peritoneal region no sac is present and the infants rarely live. In my patients with hernia in this situation the patients were obviously alive and a sac was present; the explanation of the discrepancy is probably that the herniæ in my patients had occurred in the next—but very slightly later—stage of development.

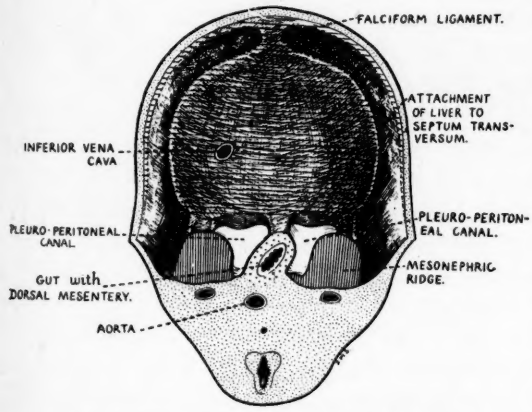

FIG. 310.—Pleuro-peritoneal canals in section.

The second stage in the development of the diaphragm occurs during the second month of intra-uterine life and may be called the 'membranous stage'. During this period the pleuro-peritoneal canal is closed by the ingrowth of its own walls, proliferation from the mesentery of the gut, and the Wolffian ridge. Its position in the adult is indicated by the costo-vertebral triangle (*see Fig.* 310). During this stage a true hernia of the diaphragm may occur, for the pleura and peritoneum are complete and have closed their respective cavities; and if any abdominal viscera are forced into the thorax at this time, a membranous sheet,

which is the developing diaphragm itself, will be found interposed between their peritoneal covering and the pleura.

The third stage in the development of the diaphragm occupies the third month. During this period the phrenic nerve preceded by the premuscle mass derived from the cervical myotomes spreads through the membranous diaphragm. The site from which the muscle spreads is indicated by the place where the nerve enters the diaphragm (*Fig.* 311), and it grows gradually through the membranous structures, *reaching the dorsal margins last of all.* (The significance of this is seen later in the description of hernia diaphragmatica transversa.) In this way the whole membranous area becomes muscularized. Subsequently a change in the distribution of the muscle occurs and the central tendon of the diaphragm is developed.

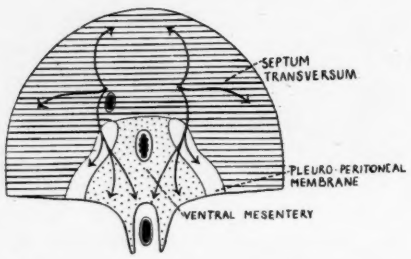

FIG. 311.—Showing where muscularization commences, and the directions of spread.

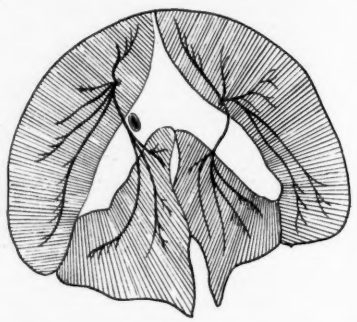

FIG. 312.—The muscular diaphragm and the phrenic nerve consist essentially of two parts—ventro-lateral and dorso-lateral.

The growing muscle surrounds the cardia, forming the hiatus (*Fig.* 312). The growth of the muscle may fail, leading to a deficiency in the muscular attachments of the diaphragm, although peritoneum and pleura separate the cavities.

In my series this growth deficiency had occurred bilaterally in the dorsal attachments in two cases and almost certainly in a third—the third I am not yet able to confirm—and probably it had occurred in three others unilaterally. This condition really amounts to an absence of the crura together with the crural attachments, and the result is to leave a gap which permits the stomach with its peritoneal investments to slide up into the posterior mediastinum in the case of the bilateral defect, and into the left pleural cavity in the case of the unilateral defect; but as the œsophagus is of normal length it slides down into the abdominal cavity just as easily—this type has been called 'hernia diaphragmatica transversa' (*see Figs.* 333–335). Its significance will be seen later. I strongly suspect that the same type of defect occurring unilaterally (i.e., lack of development of the left crus) is the cause of the left costo-vertebral—the so-called pleuro-peritoneal—type when this is found in adults (*Fig.* 313).

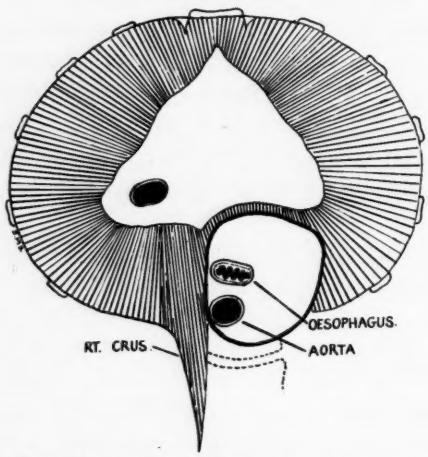

FIG. 313.—Defect in diaphragm arising from non-development of left crus, seen from below.

CLINICAL EXAMPLES OF THE VARIOUS TYPES OF DIAPHRAGMATIC HERNIA

I. HERNIA THROUGH THE RETROSTERNAL ATTACHMENT OF THE DIAPHRAGM (PARASTERNAL; FORAMEN OF MORGAGNI).

Fig. 314 is a drawing of the diaphragm from below showing the site of the defect which was the primary cause of the hernia. The aperture was 4 in. wide and lay immediately behind the xiphoid appendix of the sternum. The patient was a man aged 29. He had suffered from indigestion and epigastric discomfort for five years. The symptoms occurred in attacks lasting from four to six weeks.

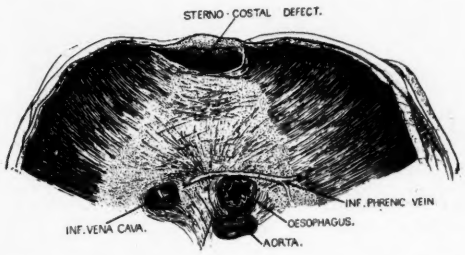

FIG. 314.—Showing site of retrosternal defect in diaphragm.

He was always conscious of a "blown-out" feeling. He was relieved by passing flatus. He had become afraid to eat. Through pain and voluntary starvation he had lost 1 stone in weight and had been compelled to give up work. A barium meal or an enema (*Fig.* 315) shows the termination of the ileum, the cæcum with the appendix, and what should be the ascending colon together with the transverse colon, in the thorax. The loop obviously enters and leaves by a narrow orifice. A second film (*Fig.* 316) shows that no splenic flexure is present; the colon on leaving the thorax descends directly to the left iliac fossa. A third skiagram has been taken laterally (*Fig.* 317). The colon had been filled with a barium emulsion, the patient placed in position, and the exposure made during the swallowing of barium emulsion. This outlines the œsophagus entering the abdomen in the normal position posterior to the pericardium, while the herniated viscera enter the thorax anteriorly immediately behind the lower end of the sternum. This patient's disability was due to nipping the segment of the alimentary canal and hampering its physiological activity.

The Sac.—In this case a sac was present. *Fig.* 318 shows the breadth of this and the extent to which the thorax was occupied. The sac and its contents occupied the anterior mediastinum, resting against the pericardium on the left and displacing the right pleura and lung backwards and to the right. The neck of the sac and its contents had spread the costosternal fibres of the diaphragm widely. After reduction the margins of the orifice were brought together easily by the sutures in the posterior half, but in the anterior half the gap was too wide and could only be closed by the aid of fascial graft sutures.

We cannot but be curious as to the period in the fœtal life of this individual when he became foredoomed to the hernia. We have three pieces of evidence :—

1. There was a defect in the diaphragm—this might have been developmental, but it might have been acquired through secondary atrophy, so that it does not help in determining whether the origin was pre- or post-natal.

2. A peritoneal sac was present; therefore the peritoneum had shut off the abdominal from the thoracic cavity before its occurrence.

FIG. 315.—Site of neck of sac. Termination of ileum, cæcum, and portion of colon in the thorax.

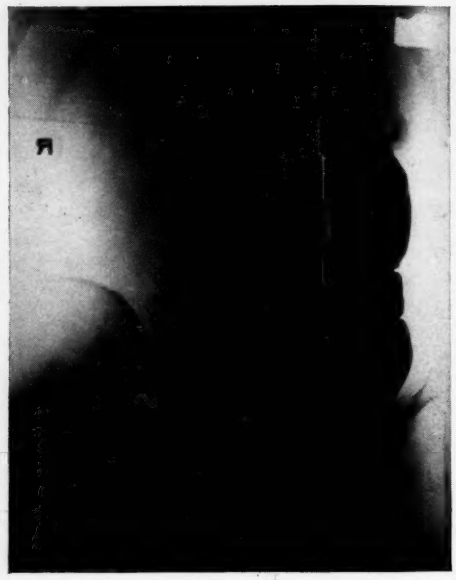

FIG. 316.—Showing absence of splenic flexure.

FIG. 317.—Lateral view. 1, Contents of sac; 2, Œsophagus; 3, Level of diaphragm

FIG. 318.—1, Terminal coil of ileum; 2. Appendix and colon; 3, Neck of hernial sac at site of the defect.

3. The hernia had occurred before the rotation of the large gut was completed, for no splenic or hepatic flexure had developed, and the cæcum had never occupied its position in the right iliac fossa.

The developmental story would be incomplete if I omitted to mention one post-operative sequence. As the sac and its contents were retrosternal, access was obtained by splitting the lower half of the sternum (*Fig.* 319) and separating the two costosternal leaves after the abdomen had been opened by a comparatively short, high epigastric incision. At the end of an extensive operation it seemed expedient to fix the cæcum to the abdominal wall just below the liver, rather than

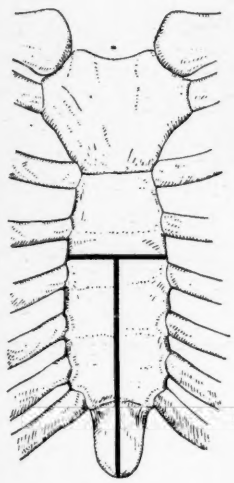

FIG. 319.—Line along which the sternum was sectioned.

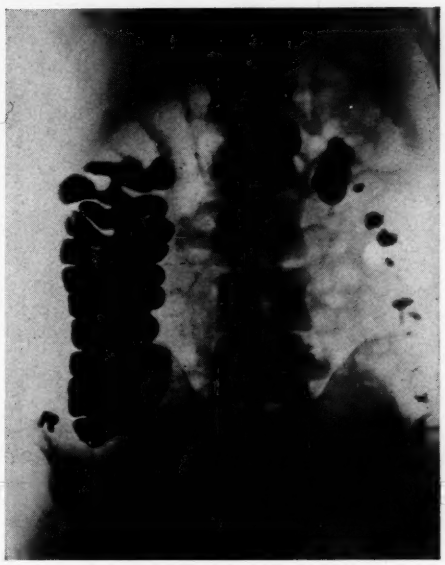

FIG. 320.—Skiagram showing that the cæcum has returned to its normal position.

prolong the abdominal incision in order to attempt to place the cæcum in a more normal situation. *Fig.* 320 from a skiagram taken four weeks after the operation shows that by that time the cæcum had migrated to the right iliac fossa. During the twenty-nine years it had sojourned in the thorax it had never lost its developmental urge to occupy its normal position.

II. HERNIA THROUGH THE LEFT DOME OF THE DIAPHRAGM.

This hernia is actually through the substance of the diaphragm, and therefore to be distinguished from those through the left costo-vertebral angle, which—at any rate in two of my three cases—were really situated *behind* the diaphragm.

Fig. 321 is a drawing showing the position of the defect. This is independent of any of the natural openings. I have two patients of this type. One was a woman of 52, whose serious symptoms were of only two or three months' duration. These rapidly increased in severity, and during this time she never became comfortable. She was afraid to take food. The pain was situated behind the sternum, in the epigastrium, and through the left thorax. Her face expressed anguish and this

distressed look never lifted. The second patient (*see Fig.* 325) is a child of five years, who has periodic attacks of pain separated by weeks or months. His appetite is normal and food does not cause pain. The elderly woman I have operated upon; the parents of the child are considering operation, but when the attacks of pain pass they hesitate.

Skiagrams of the condition in the first patient show (*Fig.* 322): (1) The œsophagus of normal length; (2) The actual cardia and small portion of the stomach in the abdomen—when outlined with barium it has the appearance of a filled champagne glass; (3) A very large middle portion of stomach in the left thorax

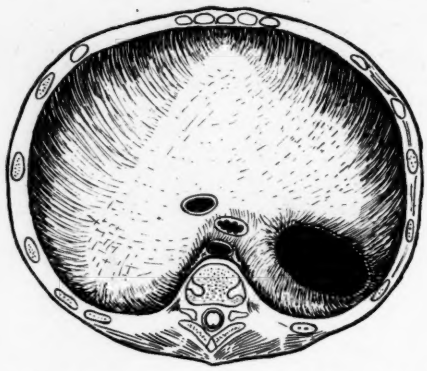

FIG. 321.—Drawing from below to show congenital defect in left half of diaphragm.

distended with air, displacing the mediastinum with the pericardium and heart to the right. *Fig.* 323 shows the pylorus re-entering the abdomen. It can be seen that the left lung is compressed into the apex of the thorax.

Fig. 323 with its explanatory sketch (*Fig.* 324) shows beautifully the cardia entering and the pyloric portion of the stomach returning through the hernial orifice. This hernia was so extensive that it might have been mistaken for the condition known as eventration, or paralysis of the left phrenic nerve with elevation of the left leaf of the diaphragm; but when the skiagrams are scrutinized it is seen that the herniated structures are narrowed at the point of entry and exit, and that although the incarcerated portion of the stomach is so large, both the cardia and the pylorus are fixed in the abdomen. This would not occur with eventration. The points of entry and exit are away from the costo-vertebral angle and imply the position of the orifice.

The skiagrams cannot show, but operation revealed, that: (1) No peritoneal sac was present; (2) Dense adhesions bound the stomach to the margins of the orifice; (3) Firmly organized adhesions bound the stomach to the compressed lung; (4) The stomach was rotated on its axis and the spleen was above the diaphragm; (5) The entire circumference of the orifice consisted of thick muscle.

The absence of a peritoneal sac implies that the defect had occurred before the membranous subdivision of the cœlomic space into pleural and peritoneal cavities; but the defective diaphragm had subsequently become completely muscularized up to the margins of the defect. The actual hernia must have occurred in the first stage of the development of the diaphragm. The condition present in this patient makes this an appropriate place to discuss the question of surgical access.

FIG. 322.—The œsophagus is seen entering the cardiac end of the stomach, which is directed cranially. The main part of the stomach is situated in the thorax and is filled with gas. This has displaced the heart to the right (shadow seen on the left of the film).

FIG. 323.—The œsophagus enters the stomach in the abdomen; the stomach at once enters the thorax. A narrow line of barium indicates its exit from the thorax, the pyloric portion of the stomach being in the abdomen. The aperture in the diaphragm is shown in *Fig.* 321.

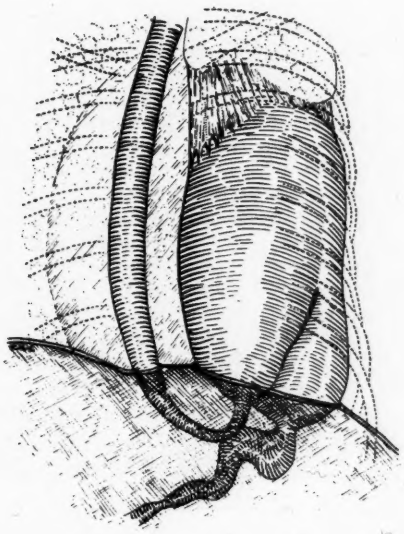

FIG. 324.—This drawing explains *Fig.* 323. It shows the adhesions between the stomach and the compressed lung. It is an exact reproduction of another film, with the adhesions drawn in.

The Approach.—Some surgeons favour the abdominal approach; others the thoracic. In this patient the adhesions of the stomach to the base of the lung, which was compressed into the apex of the pleural cavity, would have prevented withdrawal of the stomach through the orifice from the abdomen; nor could the spleen, which was adherent in the thorax, have been reduced. On the other hand, dense adhesions fixed the stomach in the neighbourhood of both cardia and pylorus to the margins of the orifice, and these would have prevented replacement of the stomach if a thoracic approach alone had been used. It was therefore necessary to open both the thorax and the abdomen. The great dilatation of the stomach would have prevented its replacement without deflation. After insertion of a pursestring suture, the stomach was emptied of its gas by a suction apparatus attached to a trocar and cannula. After the replacement of the stomach below the diaphragm, and repair of the hernial orifice, I felt sure that the patient could not for some time be happy with a stomach of this size in the abdomen. In patients where the stomach has been housed in the thorax for a long time the abdomen has adjusted itself to its absence. I had learned from patients upon whom I had operated previously that when the abdomen is suddenly asked to make room for an unaccustomed stomach—and a greatly distended one—much discomfort is induced; and this was the biggest stomach I had seen. After closing the thorax I therefore performed a gastrostomy, not for the purpose of feeding the patient but to give temporary exit to its gaseous contents. This manœuvre was justified, the patient being free from this discomfort after operation. Skiagrams following operation show the left lung completely expanded, and the stomach situated below the diaphragm.

FIG. 325.—Hernia of transverse colon.

The second patient with a hernia in this site is the child of 5 years. *Fig.* 325 shows the condition with part of the colon in the thorax. The attacks of pain only occur at intervals of some months. They are undoubtedly due to temporary obstruction of the colon. The child has not been operated upon. He is living in danger of an acute obstruction.

III. HERNIA THROUGH THE COSTO-VERTEBRAL ANGLE (LEFT)

The third anatomical site is through the costo-vertebral angle of the left side (*Fig.* 326). For reasons to be given later I consider this a more accurate designation than ' pleuro-peritoneal hiatus ' or ' foramen of Bochdalek ', at least in adult patients with a peritoneal sac present.

Screen examinations of two of the three patients of this type showed an œsophagus of normal length, and in the third this was proved to be so at operation. Other findings are :—

1. A portion of the stomach and transverse colon may occupy the left thorax (*Fig.* 327).

2. The whole stomach, including both orifices, may be in the thorax.

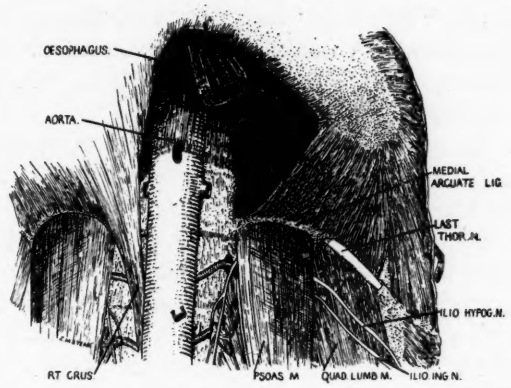

FIG. 326.—Drawing showing defect in the left diaphragm, due probably to non-development of the left crus. It was closed by peritoneum, which constituted the hernial sac.

The stomach becomes rotated so that the greater curvature is directed cranially (*Fig.* 328).

3. The stomach may be angulated over the edge of the diaphragm (*see Fig.* 330). Again, although a large sac is present, it may sometimes be empty, the

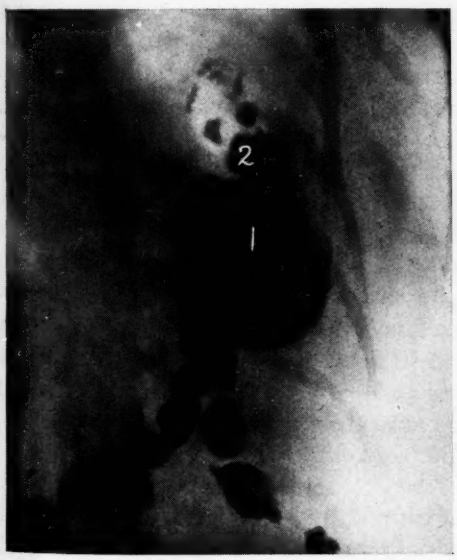

FIG. 327.—Stomach (1) and portion of colon (2) in the thorax.

FIG. 328.—The whole stomach is in the thorax, the greater curvature uppermost. 1, Pyloric portion of stomach; 2, Breast shadow.

stomach being in the abdomen. This was proved—unfortunately—in two of my three cases of this type; in one when the X-ray examination was being made; in the other at the first operation.

Each of the three patients with a hernia in this site upon whom I have operated was middle-aged. The symptoms were attacks of severe abdominal pain, often but not always brought on by taking food; so much so that one of the patients said, "I look at food, I want it badly, and I do not take it." Although these attacks were severe, the "bursting" sensation and feelings of oppression were almost worse than the pain. In one there was severe pain in the left shoulder, axilla, and arm; in another severe hæmatemesis had occurred; in all the attacks were becoming more frequent.

Portions of the clinical history of two of the three patients belonging to this type show that—as in an inguinal hernia—the contents may not always occupy the sac. When there are no adhesions and when the orifice is large, as it apparently always is in this type, gravity may tend to keep the sac empty. When symptoms are present and another diagnosis has not established their cause, grave disservice may be done to a patient unless the radiological examination includes inspection in a modified Trendelenburg position. One of these patients had been examined radiologically and sent with a diagnosis of gall-stones, and with the statement that X-ray examination had excluded any abnormality of the alimentary canal. On opening the abdomen, neither stomach, great omentum, nor transverse colon was to be seen. They occupied the thorax, and the aperture of entry was readily found. The barium-filled stomach was certainly in the abdomen and not in the thorax when the X-ray examination was made with the patient in the upright position. At operation the condition was obvious and was dealt with; but in the second case it was not obvious and was not dealt with—at least not until later and by submitting the patient to another operation.

The Sac.—In each of the three cases of this type a sac was present—and a very large one, consisting of peritoneum and pleura separated by a little areolar tissue. The pleural envelopment of the peritoneal sac was complete and well-fitting, so that I believe it had been present from an early period of development.

Margins.—Antero-laterally there is firm diaphragmatic tissue, but postero-medially when the sac is opened and the margins are examined from the thoracic side there is only pleura and areolar tissue covering the œsophagus, the aorta, and the neighbouring area of vertebra, rib, and intercostal space.

The embryology of the condition in these three patients raises an interesting problem. It is repeatedly stated that in hernia occurring through the pleuro-peritoneal hiatus no sac is present, that therefore it is a false hernia, and that the patients almost never survive. Hume stated in his 1922 Hunterian Lecture that while hernia through the pleuro-peritoneal hiatus is the commonest type—if fœtal cases are included—it is rarely met with in adult life; and that Sir Arthur Kieth had only been able to collect 21 cases in the medical museums of London, and of these only 2 survived birth by more than a few weeks. In each of my three cases a sac was present and the patients had reached middle-age. It occurs to me that a review of the embryology may explain this discrepancy. In the early phase of fœtal development the pleuro-peritoneal canal is not closed. Any slight lack of co-ordination in development before the closure could lead to displacement of abdominal organs along the open canal—there is no membrane to make a sac—the condition tending to terminate life very soon after birth. This is what is found post mortem in the great majority of infants dying from the condition, and it had led to the widely held belief which has been expressed by so many writers. The

three cases now being described would indicate that in the second period of diaphragmatic development—let us say during the second month—the pleuro-peritoneal canal is in process of being closed by membrane, but is not yet muscularized. This always remains a comparatively weak area. Protrusion of abdominal organs beginning at this stage would carry with it a peritoneal sac and push before it a pleural covering as well. This may take place slowly and may not become extreme until later life, thus enabling the individual to live, although the disability continues to increase; and it explains the presence of the sac and the age at which the condition has been found in my cases.

Etiology.—In discussing the etiology of these three cases I want to put forward another explanation which I believe is the right one, but which I cannot yet prove. In the section of this paper dealing with embryology, *Figs.* 311, 312 showed the central area where muscularization began and its line of spread from the centre to the periphery. The crura are therefore a *final development*, not an *origin* of the muscle. Operation in each of these three cases gave increasing familiarity with the region, and I now suspect that each hernia has resulted from a congenital absence of the left crus and the muscular fibres continuous with it. Certainly in the last two no muscle could be found where the left crus should have been, and no anatomical hiatus existed, a large defect in the diaphragm being present occupied by the sac. Both œsophagus and aorta passed from the thorax to the abdomen behind the sac through the defect. Both these structures were completely visible in their lower thoracic course, and, through the defect in the diaphragm, the junction of the œsophagus with the stomach was under vision. This theory is strongly supported by consideration of the case illustrated by *Figs.* 333–335 (hernia diaphragmatica transversa), where both crura were undoubtedly absent, the diaphragm having no posterior attachment in the region of the vertebral column. This absence of a postero-medial or posterior margin to the hernial orifice is of importance to the surgeon and to the patient, for there is no firm posterior attachment for the sutures; for this reason, and also because the phrenic nerve has been temporarily paralysed, the repaired diaphragm—and the fundus of the stomach—remains at a level higher than normal (*Fig.* 329).

Nevertheless symptomatic cure is obtained, the patients being completely comfortable; and a skiagram taken subsequent to operation shows that the stomach, which had been entirely thoracic and rotated on itself, is now situated in the abdomen with its axis and its function normal.

In the second case of this type the patient had been sent for operation for gall-stones. The history appeared to be characteristic and gall-stones were present. The operation note states that the stomach was abnormally shaped; two pyloric constrictions appeared to be present, one at the usual site and another three or four inches proximal to it, the intervening portion being a cylindrical tube of about duodenal calibre, but with its walls more like stomach than duodenum (*Fig.* 330).

Unfortunately, having found the gall-stones, it did not occur to me to examine the diaphragm. The explanation came later. The patient was not cured of the attacks of pain by the cholecystectomy, and a radiological examination subsequently carried out by Dr. Lindsay Locke for Dr. Gordon Lane revealed the diaphragmatic hernia. In this patient the defect in the diaphragm was very large. The stomach reached the clavicle (*Fig.* 331), but as it was completely in the abdomen at the time of the first operation it obviously could slide out of the thorax. The explanation

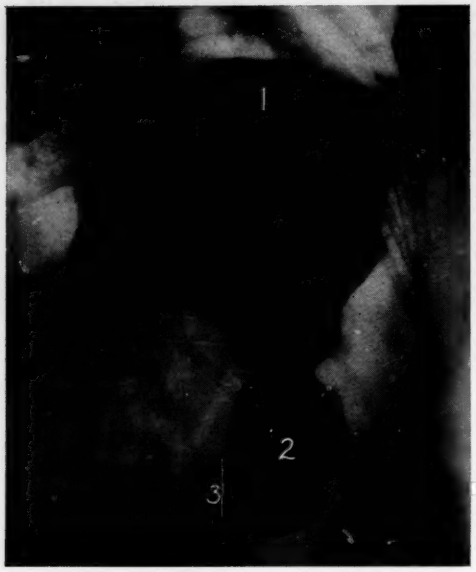

FIG. 329.—The same patient as *Figs.* 327, 328, after operation. 1, Fundus of stomach; 2, Pre-pyloric segment; 3, Duodenal cap.

FIG. 330.—Showing: 1, Air-cap in herniated stomach, which is seen angulated over the margin of the defect in the diaphragm; 2, Dome of right diaphragm; 3, Abdominal portion of stomach which was permanently narrowed as described in the text.

FIG. 331.—The fundus of the stomach (1) is seen almost reaching the sterno-clavicular articulation. 2, Colon.

of the distal narrowed portion of the stomach is possibly that the proximal portion did not empty easily and became dilated as seen in *Fig.* 330, while the distal portion only filled by overflow and remained tonically contracted. This exit by overflow is seen in the duodenum of the patient illustrated in *Fig.* 338, where the pylorus was fixed by dense adhesions several inches above the diaphragm.

IV. HERNIA IN THE REGION OF THE ŒSOPHAGUS

As stated in the classification, I have examples of hernia in this situation due to three entirely different anatomical defects. *Fig.* 332 will show at a glance the differences before the more complete description of each is given.

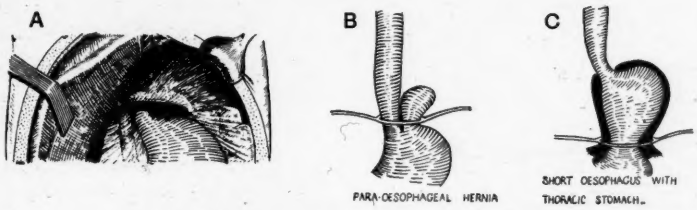

FIG. 332.—A, Congenital absence of both crura and adjoining portion of the diaphragm. The stomach slides up into the posterior mediastinum. B, Para-œsophageal hernia. C, The œsophagus terminates in the thorax and the cardiac portion of the stomach occupies the thorax.

ŒSOPHAGEAL REGION: (A) HERNIA TRANSVERSA DIAPHRAGMATICA.

This is due to non-development of the diaphragmatic crura; it is *not* a para-œsophageal hernia occurring through the hiatus. The anatomical hiatus, which should be formed by the fibres continuous with the crura, does not exist. There

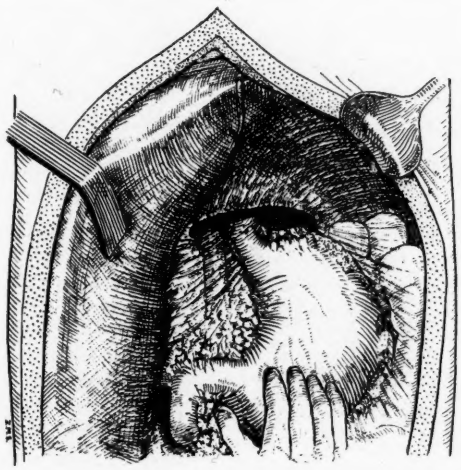

FIG. 333.—Transverse diaphragmatic hernia in which the stomach slides up and, unless held down, occupies a position in the posterior mediastinum as shown in *Fig.* 334.

is no posterior attachment of the diaphragm in the region of the aorta, the œsophagus, and the vertebral column. There is a gap in the diaphragm 4 to 5 in. in lateral measurement and 2 to 3 in. in antero-posterior measurement. This defect is shown in *Fig.* 333. This drawing shows the left lobe of the liver

retracted and the stomach withdrawn from the sac which occupied the posterior mediastinum, and represents what was seen at operation. If the hand let go the stomach, the latter at once slipped up through the defect. The concavity of this reniform defect is formed by the body of the twelfth dorsal vertebra. The hernial sac protrudes through this into the posterior mediastinum, and the defect is bilaterally symmetrical (*Fig.* 334). The œsophagus is of normal length, as shown in *Fig.* 335, and at operation its junction with the stomach was clearly defined when the latter organ was—quite easily—drawn down into the abdominal cavity.

FIG. 334.—The stomach occupies the sac in the posterior mediastinum.

Consideration of these two skiagrams suggested the type of hernia. This patient was 54 years of age and she had been under observation for many years. A short œsophagus had been diagnosed from X-ray examination elsewhere. Our examination (*Fig.* 335) disproved this. She had suffered from symptoms for many years and their severity was increasing. Dyspnœa was distressing, and a feeling of tightness and pain was always present across the lower sternal region. Turning in bed caused such distress that she had adopted the plan of sitting up, turning in the desired direction, and then lying down again. The symptoms and the examinations showed that the hernia was increasing in size. This is to be expected, as with every inspiration suction is exerted and, as well, hydrostatic pressure is directed on to the contents of the hernial sac with the constantly recurring expulsive efforts of the body.

FIG. 335.—Œsophagus of normal length. The stomach is in the posterior mediastinum.

At operation, by dividing the left coronary ligament of the liver and retracting the left lobe, the region was completely under vision and could be readily examined. The stomach was easily withdrawn from its sac in the thorax; the reniform orifice of the sac was clearly defined; the aorta and the œsophagus were visible and palpable behind the peritoneum of the sac.

This type would seem to be due to the absence of development of both crura and the adjoining part of the diaphragm, leaving a gap between a well-defined and

perfectly free posterior margin of the diaphragm which bounds the sac anteriorly and the vertebral column and adjoining part of the paravertebral grooves which bound it posteriorly. Through this gap the peritoneal sac ascends into the posterior mediastinum. The defect is therefore behind the incomplete diaphragm. In closing the gap by sutures a firm grip can be obtained anteriorly, but, as in the last type, there is no strong structure posteriorly into which the sutures may be inserted. In spite of this, closure of the gap has given complete relief to the very distressing symptoms.

In this patient gall-stones were present. The operation had been an extensive one, and I considered it expedient to leave them to be dealt with at a later date, if necessary.

In another patient, whose symptoms pointed to gall-stones, the X-ray examination (*Fig.* 336) revealed a diaphragmatic hernia as well as a pathological

FIG. 336.—The upper loculus is in the thorax.

gall-bladder. Operation for the gall-stones gave the opportunity of examining the hernial orifice, and it proved to be similar to the one just described. As in this case the symptoms were due to the gall-stones alone, they were dealt with and the hernia left. The patient's husband is a medical practitioner and she can be kept under observation.

I have seen a third patient whose hernia I believe to be of this type, absence of the crura leaving a gap between the posterior margin of the diaphragm and the vertebral column, which allows the stomach to slide up into the thorax carrying the lower end of the œsophagus up with it (*see Fig.* 349). This patient suffers from attacks of intense oppression and dyspnœa which last for a varying number of hours. These attacks are separated by several months of freedom. The condition in this patient has not been confirmed by further X-ray examination nor by operation.

Œsophageal Region: (b) Para-œsophageal Hernia

The second type of hernia in the œsophageal region is the para-œsophageal. The œsophagus is of normal length. The hiatus is present, but it becomes dilated. A hernial sac exists, or is acquired, passing up through the hiatus, lying beside the œsophagus. *Fig.* 337 illustrates the condition. This type has been well described, but each of my two cases has some special features. In the first the symptoms became urgent at the age of 77 and were so severe that the patient retched and vomited constantly and could not retain even arrowroot. Operation was therefore a matter of urgency and was carried out July 2, 1928. The hernia was approached by the abdominal route. This lady is now 82 years of age and, six years after operation, enjoys life—and her cigarettes—very thoroughly.

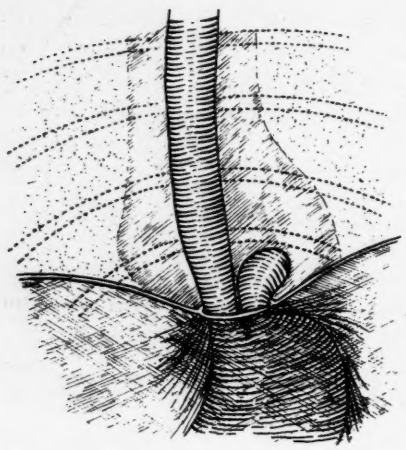

Fig. 337.—Initial stage in formation of para-œsophageal hernia.

The second patient, aged 50, had never been happy for over twenty years. She suffered from attacks of pain "like acute indigestion", often with sickness. Diet restrictions had to be made more rigid in recent years; she could never go out to dinner. Vomiting formerly gave relief, but latterly discomfort was never absent. The appendix had been removed. Subsequently gall-stones were found present and were removed. X-ray examination from time to time showed an increasing amount of the stomach in the thorax. The pylorus was evidently fixed well above the level of the diaphragm and its outlet so hampered that stomach contents only left it in a trickle (*Fig.* 338), the stomach itself becoming increasingly distended.

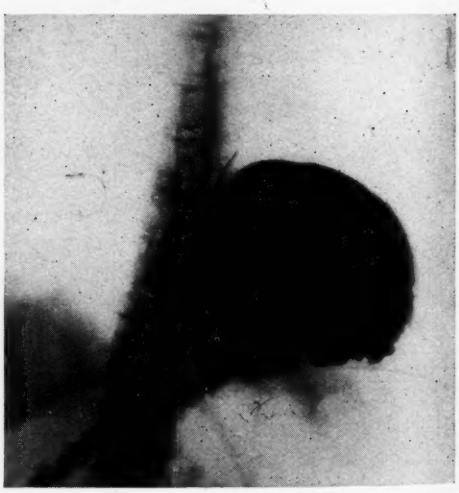

Fig. 338.—Stomach with greater curvature uppermost; pylorus fixed above diaphragm; barium leaving pylorus in a thin trickle.

Operation. — The abdomen was opened through a left subcostal incision. Adhesions, fixing the small portion of the stomach still remaining in the abdomen, were so dense that it was impossible to withdraw the organ from the thorax. A thoracic approach was therefore made. The sac was adherent to the pericardium and to the base of the lung. After freeing the sac sufficiently to open it safely, the stomach was found folded on itself, the greater curvature uppermost, and adherent almost all around the neck of the sac. The adhesions were especially dense in the pyloric region, which was fixed several inches

above the diaphragm. All these features are seen in the skiagrams (*Fig.* 338). Separation of the adhesions was continued from the abdominal side, but it was still very difficult to free the pylorus, which remained firmly anchored above the diaphragm, and until this was accomplished it could not even be seen how the stomach should lie. When the adhesions were completely divided the pylorus at once fell into its natural position and—except for its dilatation—the stomach appeared normal. The operation had been long and difficult, and it was essential to close the sac and the diaphragm from above in the speediest manner. The skiagrams showed, and the operation findings confirmed, that this stomach could not pass on its contents except in a small trickle. It could only be dealt with by a double approach.

Œsophageal Region: (c) The Short Œsophagus Type of Hernia

The third type of diaphragmatic hernia occurring in the œsophageal region is that associated with a congenitally short œsophagus, the cardia and portion of the stomach being situated within the thorax. Some have dismissed this as being a simple extension of the gastric mucosa through the cardia into the lower end of the œsophagus, and of no consequence. Gastric mucosa may extend through the cardia, but that is not the condition present in 14 patients whom I have seen in the last few years, and described by Bailey,[8] Akerlund, Woodburn Morison, Hurst, Monkhouse, Montgomery, and others. It is astonishing how frequent this condition is. It is definitely the cause of symptoms, not infrequently distressing and sometimes fatal. The embryology has been described by Keith. The stomach originally is almost cervical. Normally the œsophagus elongates and the stomach migrates tailwards until it reaches its position below the diaphragm. In the cases under discussion the œsophagus failed to elongate adequately, and the stomach is partially arrested in the posterior mediastinum (*Fig.* 339). This arrested portion of the stomach is surrounded—except at the actual cardia—by a peritoneal sac, so that a true hernia results.

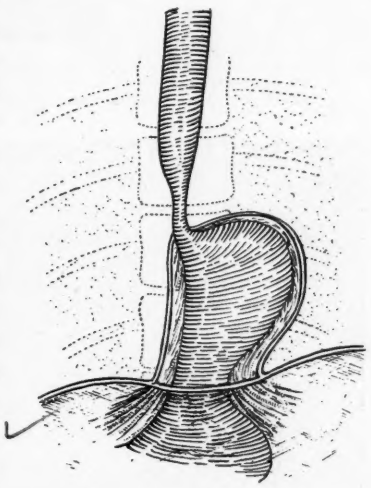

Fig. 339.—Congenital short œsophagus : early stage.

If the condition remained at this stage, possibly little harm would result, and indeed it must exist in a number of people who never suspect it; but as it has only been discovered in the patients of myself and others because a reason for some disability was being looked for, we must believe that sooner or later it begins to give trouble, and there is ample evidence that the trouble is progressive.

Anatomy.—That it should be progressive is obvious when we consider the anatomy. The diaphragm should enclose the narrow cardia within its hiatus, but it encloses instead the circumference of the fundus of the stomach by means of a large opening. The stomach is therefore hour-glass-shaped, the cardiac loculus being within the thorax and the pyloric loculus within the abdomen. By radioscopy barium emulsion is seen to flow readily from one sac into the other

(*Fig.* 340). Two forces act on this continuously. Every expulsive effort of the body is exercising hydrostatic pressure on the stomach and its contents, pushing it up, and during every inspiration it is being drawn into the thorax by suction.

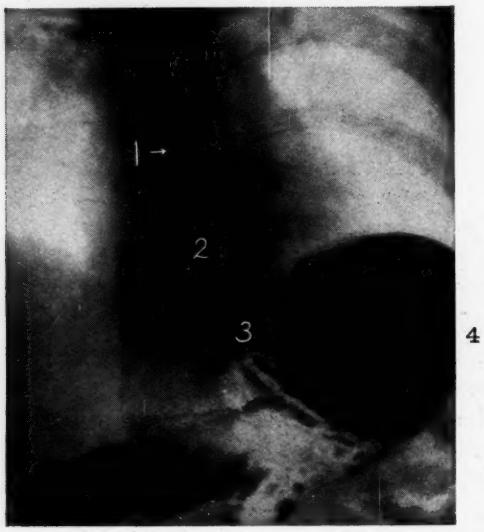

FIG. 340.—1, Cardia; 2, Proximal loculus of stomach in the thorax; 3, Level of diaphragm 4, Distal loculus of stomach in the abdomen. A larger thoracic loculus is shown in *Fig.* 342.

FIG. 341.—1, Œsophagus; 2, Cardia; 3, Thoracic loculus; 4, Dome of left diaphragm.

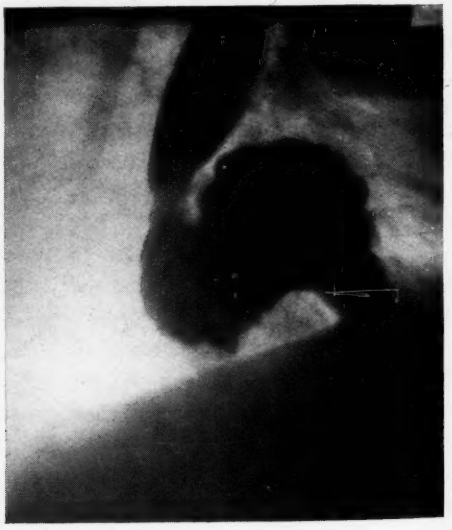

FIG. 342.—A large thoracic loculus and rotation beginning.

The diaphragmatic opening becomes more dilated, and progressively more of the stomach comes to occupy the thorax. As this happens, the stomach tends to rotate on its own axis, probably because the greater curvature is longer and more free than the lesser curvature; and—through fixation by adhesions—it may also

become twisted on its long axis. Skiagrams of three patients (*Figs.* 341–343) show the successive stages of this passage into the thorax and rotation.

Fig. 341 shows an early stage with the thoracic segment small and the axis of the œsophagus and the stomach normal. *Fig.* 342 shows a later stage—the thoracic segment of the stomach is increased at the expense of the abdominal segment and rotation is beginning. *Fig.* 343 shows a very late stage. The drawing (*Fig.* 344) explains the film, which was given to me by Dr. A. F. Hurst. The

FIG. 343.—Practically the whole of the stomach is in the thorax, and rotation is almost complete.

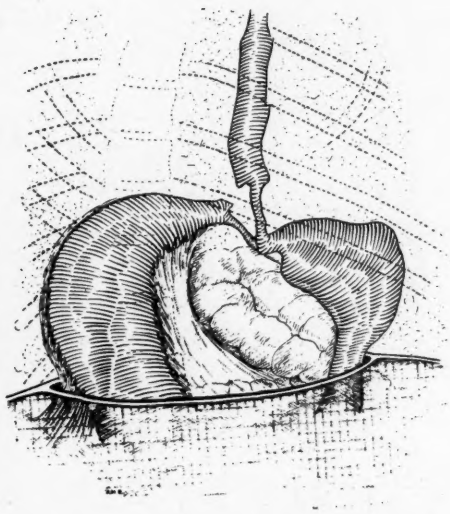

FIG. 344.—Drawing from film to explain *Fig.* 343.

patient was very ill and the skiagram was taken under difficulties, but it shows the short œsophagus and the stomach in the thorax with its greater curvature uppermost. Some bowel has been drawn or forced up into the thorax. The stomach is twisted or obstructed in its middle third, resulting in two loculi. Emptying the proximal loculus by an œsophageal tube gave relief. It was impossible to empty the distal loculus.

It would not add to the value of this article to include skiagrams of the other patients; but I have films of all of them, and some are used to illustrate pathological changes incidental to the condition.

Pathology.—Apart from increasing herniation, pathological changes may, and do, occur: (1) At the cardia; (2) In the œsophagus; (3) In the stomach.

As the cardia is situated well above the diaphragm in the thorax it is very accessible for X-ray examination. The first patient seen with this condition came in 1930 bringing a skiagram (*Fig.* 345). From this a diagnosis of carcinoma of the œsophagus had been made. I knew he had suffered from dysphagia for five years previous to this, and therefore felt sceptical about the diagnosis. X-ray and œsophagoscopic examinations had been made over this period without result. I then had the examination carried out in the Trendelenburg position, when the condition was obvious (*see Fig.* 340). This patient has been watched for four more years—nine in all. Dysphagia has been at times extreme with choking and return

of food. Is the dysphagia due to spasm (cardiospasm or achalasia), or is it due to organic stricture?

Dilatation.—That cardiospasm or achalasia occurs at the cardia (situated in the thorax) with dilatation of the œsophagus is shown by *Fig.* 347.

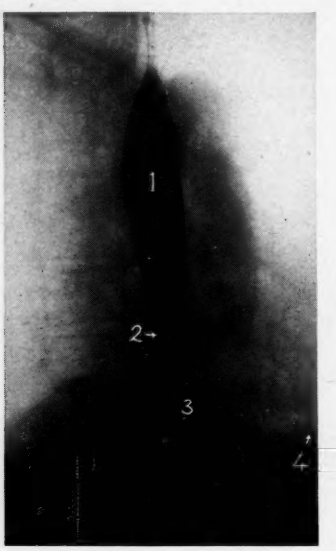

FIG. 345.—1, Dilated œsophagus; 2, Cardia; 3, Thoracic stomach. (1930.)

FIG. 346.—The same patient as *Fig.* 345 in 1933. Each dome of the diaphragm is well seen with portion of the stomach above.

FIG. 347.—Dilated œsophagus. Cardia in the thorax. Portion of stomach in the thorax. Both domes of the diaphragm are seen.

Stricture.—The clinical, radiological, and pathological evidence indicates that the stricture may be organic. Clinical, because a small mercury bougie would pass in the beginning and a larger one would not—now I cannot pass a mercury bougie at all; nor can I in several other patients. The X-ray evidence is seen in *Fig.* 348, a skiagram which shows the dilatation above—not to an extent sometimes seen in cardiospasm certainly—and in addition we see an irregularity in the œsophagus immediately above the constriction which œsophagoscopic examination shows to be due to ulceration. Pathological evidence has been obtained from actual inspection and palpation at operation. This confirmed that organic constriction was present. One patient had been admitted as a case of œsophageal obstruction. She improved and was discharged. She was later re-admitted in

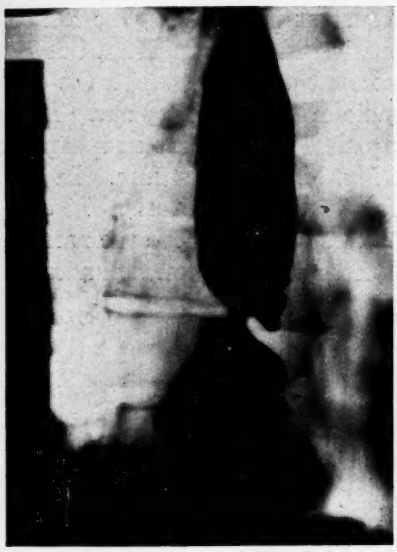

FIG. 348.—Showing dilated œsophagus, a narrow stricture at the cardia with an ulcer above the narrowing, the cardiac portion of the stomach in the thorax.

FIG. 349.—The œsophagus is seen entering a large thoracic loculus of stomach. The diaphragm is clearly seen, as is the pyloric portion of the stomach and the duodenum.

a condition of acute obstruction, thought to be too ill for X-ray examination, and a gastrostomy was performed. While this was being carried out by a colleague the stomach and diaphragm were examined, and the hernia with its peritoneal sac was discovered. X-ray examination revealed the true diagnosis. I had hoped to bring the stomach up to the œsophagus above the stricture, after paralysing the left phrenic nerve. This was impossible, but through a thoracic approach I dissected the stenosed area cleanly and found it to be about 3 cm. long, fusiform, and very firm.

One patient with short œsophagus has never, up to the age of 27, been able to swallow anything firmer than mince. Attempts to pass a mercury bougie have failed. He has to give his whole attention to his meal, and takes a long time over it. He can never go out to meals, and he is undersized. I have recently seen a child of 12 who has never been able to swallow properly. In this child the results of malnutrition are obvious.

Dysphagia is not due solely to spasm or stenosis. Remembering the anatomy

and the pathological physiology it will be understood that the thoracic loculus of the stomach will be sometimes distended. If the stomach is angulated across the diaphragmatic opening, or even partially rotated, the distension of the thoracic sac will be increased, maybe very greatly, and it may press on or kink the lower end of the œsophagus, causing dysphagia, or on the pericardium, causing oppression and dyspnœa. I regard this as the reason why the dysphagia is sometimes so strangely inconstant. It may appear to be complete in recurrent attacks, and later the patient may swallow mince and soft foods readily. I have also known the attacks of dyspnœa and of what the patient calls " unendurable oppression " occur only once or twice a year, the radiogram showing a large loculus of stomach in the thorax (*Fig.* 349).

Ulceration.—This has been shown in the œsophagus immediately above the stricture (*see Fig.* 348). It is associated with constant pain around the left costal margin. I have not had a case of gastric ulceration in this condition, but Hurst and his co-workers have published a detailed account of two in which the clinical records—including severe hæmatemesis—the radiological evidence, and the post-mortem findings, were complete. Two of the patients with short œsophagus and severe dysphagia have been under the care of Mr. V. E. Negus also. In one of these the œsophagus was filled with fluid, as may occur in achalasia. In each of them endoscopy revealed the presence of some ulceration just above the narrowing, and in each it was possible to pass a dilating bag through the narrowing under vision and dilate it.

In conclusion, I have operated upon 8 patients with diaphragmatic hernia in whom the œsophagus was of normal length; 6 of these are cured; one had complete relief of symptoms but died of a pulmonary embolus ten days later. In the last one operated upon recently pneumonia occurred in the lower lobe of the opposite side—that is, the side not operated upon. This did not resolve, and a little over four weeks after the operation the patient died. A post-mortem examination was permitted. The left lung—the side from which the rib had been excised—had expanded. The diaphragm had healed and the line of suture where the hernia had been closed could not easily be found. The œsophagus entered the abdomen normally, and the stomach, which had been entirely in the thorax, occupied its normal abdominal position. The operation had achieved cure of the hernia and restoration of the stomach to the abdominal cavity. Pneumonia has, naturally, to be regarded as a possible complication of the operation. Patients with short œsophagus and partial thoracic stomach suffer in diverse ways, and treatment must in the main be symptomatic. Some only require occasional advice. In some the passage of a mercury bougie is sufficient. In some a dilating bag should be passed under vision.

Experimental work recently carried out by G. C. Knight,[9] late House Surgeon to the Surgical Professorial Unit, St. Bartholomew's Hospital, at the Buckston Browne Research Farm of the Royal College of Surgeons, has given hope that excision of the sympathetic plexus surrounding the cœliac axis may relieve the cardiospasm (or achalasia) where this has not already resulted in organic stricture.

In diaphragmatic hernia the symptoms of the condition simulate those due to gall-stones, and it is interesting that in the 11 patients with œsophagus of

normal length and herniation of the stomach, gall-stones have been found present in 5.

It should not be assumed that operation can be carried out in cases such as these without risk, or that convalescence is always smooth. The difficulties of the operation vary greatly with the situation of the defect, and with its accessibility, and this will naturally affect the convalescence.

SUMMARY

1. Cases of diaphragmatic hernia are less rare than is generally recognized.

2. The type associated with short œsophagus is by no means uncommon.

3. The symptoms may be very distressing and are often grave.

4. The symptoms are such that they strongly suggest their origin.

5. X-ray examination can do much more than determine the presence of a hernia; by careful posture of the patient and a planned technique the type and site can be determined.

6. In cases with an œsophagus of normal length an operation can be performed that frees the patient from danger and completely relieves the symptoms. The operation is not without some risk. This is not greater than one would expect, while without operation the symptoms are very distressing and the risk of a fatal termination is probably more frequent than when an operation is performed.

7. In cases with short œsophagus and thoracic stomach a radical operation to cure the condition has not yet been carried out, but much can be done to ameliorate the condition.

I am indebted to the following radiologists for the excellent skiagrams which illustrate this article: Drs. Lindsay Locke, Stone, Finzi, Simon, Bull, Coldwell, and Shanks.

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CONGENITAL HERNIA THROUGH RIGHT DOME OF DIAPHRAGM

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ALTHOUGH diaphragmatic hernia is not a particularly rare condition, several features in the case about to be described appear to justify recording it: (1) The hernia, almost certainly congenital in origin, was the cause of acute intestinal obstruction in a man aged 70 years, who had never previously suffered from his defect. (2) The hernia occurred in the right dome of the diaphragm. This situation is stated to be the least common of the various sites at which herniation may occur. It is also the type of hernia which is the most difficult to explain on embryological grounds (Hume[1]).

D. C., male, aged 70, was admitted to the General Hospital, Birmingham, under Mr. J. B. Leather, on Nov. 8, 1933.

HISTORY.—The patient complained that his bowels, previously regular, had not been opened for the past six days. During this period he had suffered from general abdominal pain, had vomited frequently, and had been hiccuping during the last few days. He had previously been perfectly healthy and had never been troubled by indigestion or constipation. Many years ago he had had a kick in the chest when he had fallen from a horse.

ON EXAMINATION.—The patient seemed to be in good general health. The abdomen was markedly distended, especially centrally and in the epigastrium. There was general tenderness. Free fluid was detected.

OPERATION.—Under general anæsthesia I opened the abdomen by a sub-umbilical right paramedian incision. Blood-stained free fluid was present. The whole of the small intestine was distended and congested. The cæcum was not present in the expected position in the right iliac fossa, and on searching for it towards the hepatic flexure, a circular opening was felt in the right dome of the diaphragm. Through the opening about the last 3 ft. of small intestine had passed into the right pleural cavity, and the constriction due to the margins of the diaphragmatic opening was the cause of the intestinal obstruction. The cæcum was drawn up immediately below the diaphragm, and the appendix had accompanied the small intestine through the opening.

The hernia was reduced without difficulty, and the affected loop of intestine was found to be viable. On withdrawing the intestine from the hernia, the right lobe of the liver, which had been dislocated to the left, returned to its normal position, thus guarding the opening in the diaphragm. The abdomen was closed.

The patient died, apparently from paralytic ileus, a few hours after the operation.

POST-MORTEM EXAMINATION.—

Thoracic Viscera.—These were normal.

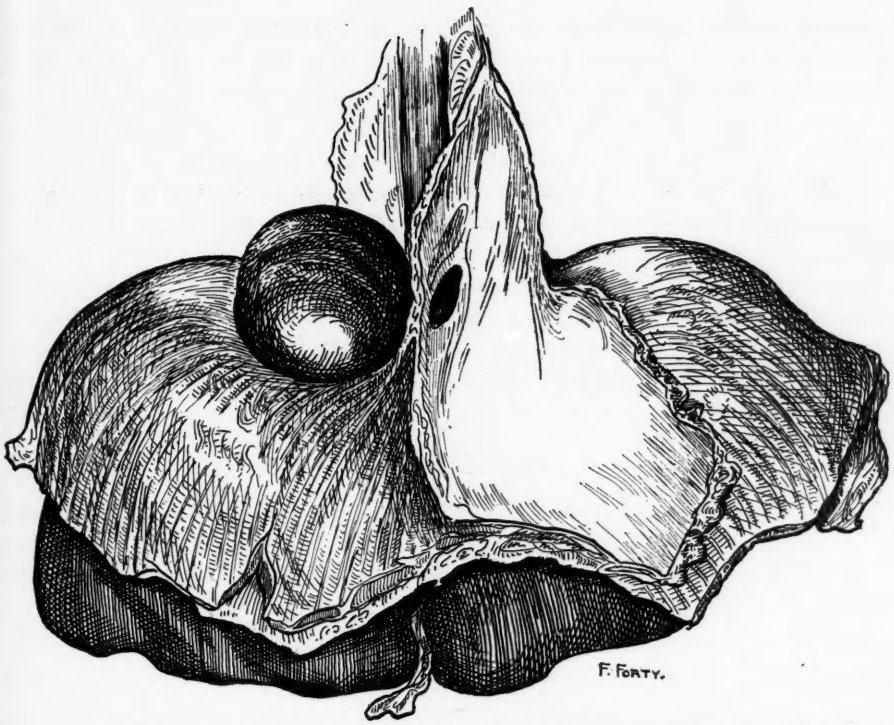

FIG. 350.—Appearance of the upper surface of the right lobe of the liver herniated into the right pleural cavity.

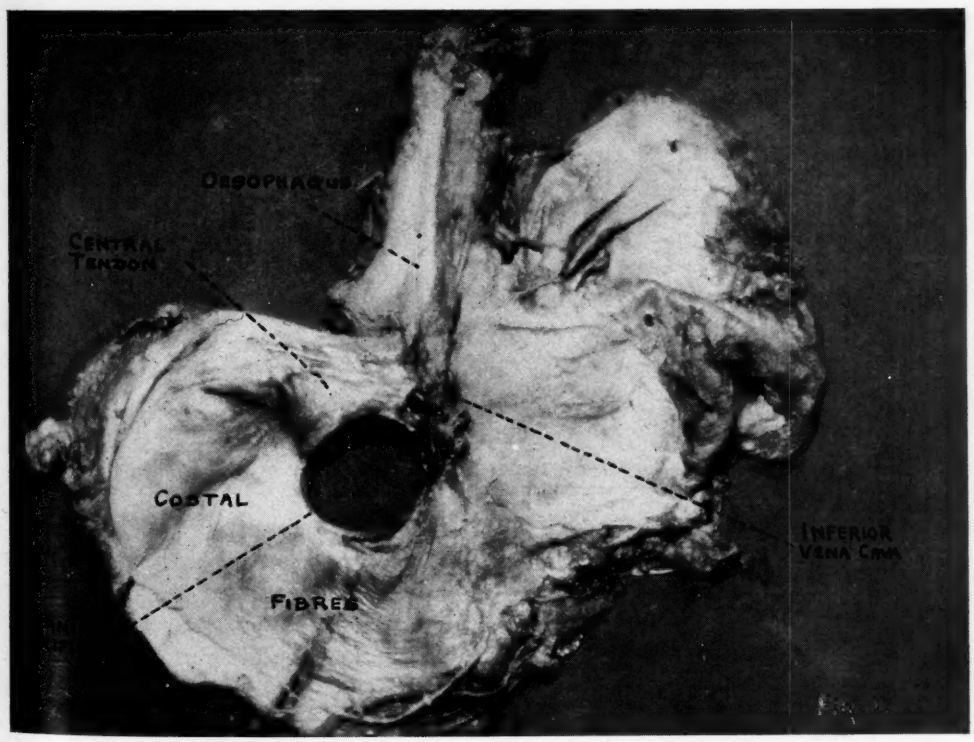

FIG. 351.—Photograph of upper surface of diaphragm, removed from liver to show the opening in the right dome. The œsophagus is seen posteriorly.

Abdomen.—The small intestine was distended throughout, and the constriction groove from the strangulation was clearly seen. The cæcum was very mobile, and now occupied the right iliac fossa. The other abdominal viscera were normal, except that a portion of the upper surface of the right lobe of the liver was herniated through the opening in the diaphragm, which it completely filled (*Fig.* 350).

Diaphragm.—An almost circular opening, 2½ in. in diameter, was present in the right dome (*Fig.* 351). It was situated immediately to the right of the pericardium. It was bounded posteriorly by the right leaf of the central tendon, and anteriorly and laterally the costal muscle fibres of the diaphragm ended in its margin. Through the opening the pleural and peritoneal cavities communicated freely. No hernial sac was present. The pleural and peritoneal serous membranes were continuous over the margin of the opening, which was perfectly smooth, and free from adhesions.

DISCUSSION

Hume[1] classifies diaphragmatic herniæ into: (1) Congenital; (2) Acquired—(*a*) non-traumatic, (*b*) traumatic.

Our knowledge of congenital diaphragmatic herniæ may be briefly summarized by the statement that they most frequently occur at the site of the embryonic pleuroperitoneal canals, where there is a failure of fusion between the costal and vertebral (crural) sets of muscle fibres (*Fig.* 352). Such a hernia is more frequently

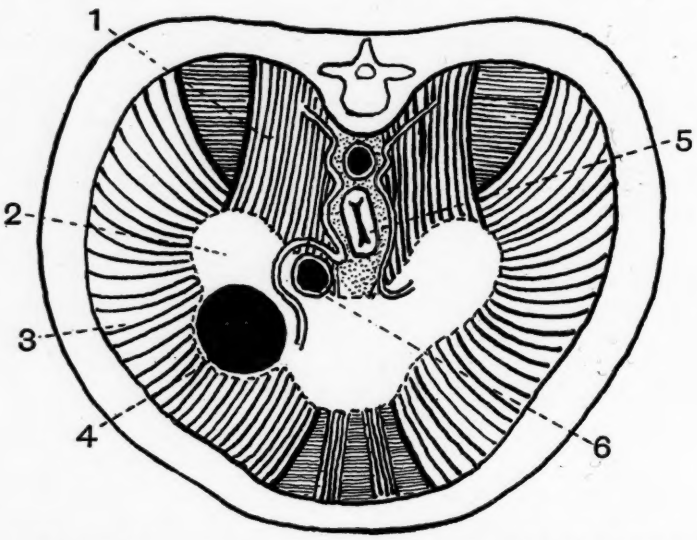

FIG. 352.—Diagram of upper aspect of diaphragm to show relation of opening to the central endon, costal muscle fibres, and pericardium. 1, Vertebral fibres; 2, Central tendon; 3, Costal fibres;, 4, Hernial orifice; 5, Œsophagus; 6, Inferior vena cava.

seen on the left side, perhaps because the diaphragm is not here supported by the liver to the same extent as it is on the right. Occasionally, congenital herniæ occur through other openings, such as that for the œsophagus, and complete absence of the left half of the diaphragm occurs in a number of cases. Hernia through the right leaf of the central tendon, on the other hand, seems to be particularly rare.

Keith[2] described 34 specimens of diaphragmatic herniæ which he found in various London museums, and of these only 2 were through the right dome. One had a sac, and the other, occurring in a child, had no sac, the pleural and peritoneal cavities communicating freely through the opening, which was occupied by a process of liver projecting into the right pleura. This case appears to correspond exactly to the one recorded in this communication. In his description of these two cases Keith states that there is little doubt that they are congenital in origin and that they were produced by an abnormal development of the liver within the septum transversum of the embryo.

Hume,[1] discussing those herniæ which occur at the site of insertion of the muscle fibres of the diaphragm into the central tendon, suggests that these may arise from a sudden forceful contraction of the diaphragm resulting in a rupture of the muscle fibres from their insertion. He accordingly infers that these herniæ through the dome of the diaphragm which are provided with a sac belong to his "acquired non-traumatic" group, but, in agreement with the opinion of Keith quoted above, he believes that herniæ occurring in this situation without the presence of a sac are congenital in origin. Hume reserves his "acquired traumatic" group for herniæ resulting from direct penetrating wounds of the diaphragm, such as those caused by the ends of fractured ribs, and emphasizes that adhesions are almost always present at the margins of such an opening.

CONCLUSION

In the light of the available evidence concerning the formation of diaphragmatic herniæ, the case here recorded appears to be one of congenital origin occurring through the right dome.

I am indebted to Mr. J. B. Leather for permission to record this case, and to Professor Lockhart for his assistance and advice.

REFERENCES

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[2] KEITH, ARTHUR, *Brit. Med. Jour.*, 1910, ii, 1297.

INTESTINAL HERNIATION THROUGH A MESENTERIC HIATUS

By E. S. J. KING,
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FROM time to time many peculiar forms of intestinal obstruction have been described. Some of these are but anatomical or pathological vagaries. Others, though very rare, show features of special interest, and one of these is here described. Several years ago I saw the following case:—

Case 1.—A female, aged 56 years, complained of abdominal pain of a colicky type, umbilical in position, associated with vomiting and complete constipation, which had been present for three days. For six hours the pain had been more severe. She had had no previous illnesses of note. On examination there was generalized distension, showing a 'ladder pattern'. Her general condition was fairly good. Enemata gave no result.

Laparotomy was performed and a herniation of the second last loop of ileum through the mesentery of the last loop was found (*Fig.* 353). The strangulated loop was markedly distended and the wall was bluish. The hiatus in the mesentery had a definite free fibrous margin in half of its extent; in the remainder the bowel was adherent to the ring. The mesentery through which the gut passed was damaged during reduction of the loop, and excision of both loops was performed. An anastomosis between the ileum and the cæcum (anterior tænea) was made. The patient made an uninterrupted recovery.

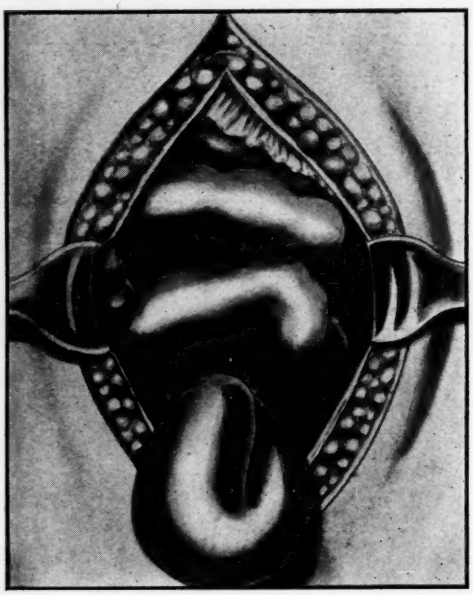

FIG. 353.—*Case* 1. The appearances found at operation (first case) showing herniation of the second last loop of ileum through a hiatus in the mesentery of the last loop.

The formation of such hiatuses in the mesentery seemed difficult of explanation. The usual hypotheses are that they may be: (1) Due to operation, an opening in the mesentery being incompletely closed; (2) Due to injuries which rupture the mesentery; and (3) Congenital defects. This patient had not had any operation performed and gave no history of abdominal injury. The third suggestion, in the absence of any direct evidence from fœtal study, affords me, personally, no satisfaction.

Frequently the causes of conditions are divided into 'congenital' and 'acquired' varieties. This use of these terms is wrong in so far as it necessitates an attempted comparison between factors of two different kinds. The term 'congenital'

presupposes that the condition is present at birth, and 'acquired' indicates that the causal factor is extraneous in origin. Thus an attempt is made to compare a time-factor with a true etiological factor. Gradually, no doubt in order to overcome this difficulty, the term 'congenital' has been used in the etiological sense and to mean an inherited factor. Such usage can only be misleading.

The etiology of groups of conditions should, then, be divided into 'hereditary' and 'acquired', according to whether the etiological disturbance is intrinsic in or extrinsic to the tissues. Acquired conditions may occur in either antenatal or postnatal life, and if the former are referred to as being 'congenital'—and of course they are congenital in the time sense of the term—it must be appreciated

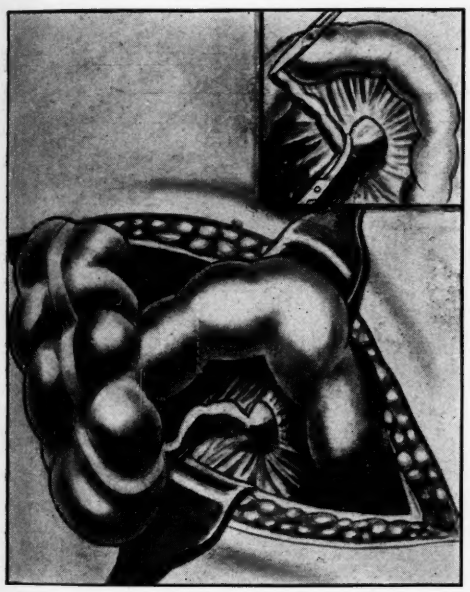

FIG. 354.—*Case* 2. The appearances seen at operation. The layers of the abdominal wall are not shown. The appendix is seen lying attached to the inferior aspect of the mesentery of the last loop of ileum. At the tip of the appendix is a bulbous structure. *Inset*: The appendix being removed by retrograde method and a forceps applied to bulbous area.

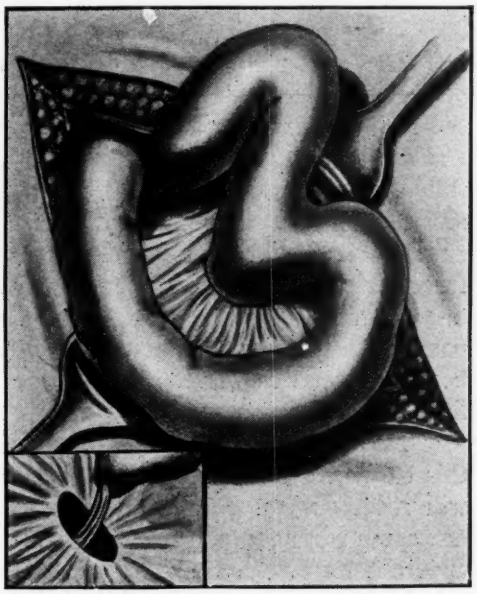

FIG. 355.—*Case* 2. The cæcum returned to the abdominal cavity and the last loop of ileum turned over (cf. *Fig.* 354) so that the mesentery of the last loop of ileum can be viewed from above. The second last loop of ileum is seen to be attached to the mesentery. *Inset*: Traction resulted in the bulbous structure (*Fig.* 354), to which an artery forceps was attached, being drawn through the mesentery.

that the term only indicates the period at which they occur and does not give any indication of the cause of the disease.

For these reasons the 'congenital' origin of the hiatus in the mesentery was, at least temporarily, dismissed.

At intervals, this case was given much, albeit fruitless, consideration. Recently, however, observations on another case suggested possible explanations of earlier findings.

Case 2.—A female, aged 30, was admitted to hospital suffering from an attack of acute appendicitis. She had had pain in the right iliac fossa for three months prior to admission.

At operation the appendix was found to be inflamed and attached to the inferior aspect of the mesentery of the last loop of ileum (*Fig.* 354). Owing to difficulty in separation it was removed by the retrograde method (*Fig.* 354, inset). When almost

completely freed the tip was found to be markedly bulbous and strongly attached to the mesentery.

Further dissection showed that the bulbous portion passed through a hiatus in the mesentery. At this stage the appendix suddenly separated at the junction with the bulbous portion, which had a curiously vascular soft wall. A forceps was placed on the bulbous portion. Examination of the appendix showed that the end was not open but was apparently the true tip of the organ and that the bulbous part was extraneous.

The last loop of ileum was now turned over (*Fig.* 355) and the second last loop was found at one point to project through the hiatus in the mesentery of the last loop. When traction was exerted, the invaginated portion and the attached forceps were pulled through (*Fig.* 355, inset) from the far side. A small opening in the bowel was over-sewn. It was noticed that the mesentery in the region of the hiatus was curiously avascular and was thinner though somewhat tougher than usual.

The patient made an uninterrupted recovery.

The sequence of events in this case appears to be as follows: An attack of appendicitis resulted in the attachment of the organ to the ileal mesentery. As the result of the spread of inflammation from this, obliteration of the blood-vessels and fibrosis resulted in avascularity of the area and the formation of a tough though thin area. Spread of the inflammatory process through the mesentery gave rise to attachment of the second last loop of ileum to the mesentery, and with subsequent fibrosis the bowel became drawn into apposition with the affected mesenteric area and then into juxtaposition with the tip of the appendix. The disappearance by atrophy of a small part of the mesentery then allowed of the passage of the piece of bowel. Of course alternatively the mesentery may have been destroyed during the acute stage of the inflammation, but this is immaterial from the point of view of the present thesis.

Two well-known and well-recognized phenomena allow of the correlation of this case with the former: (1) Once the beginnings of a hernia are present, this will readily increase in size; and (2) Adhesions and evidences of inflammation disappear from the peritoneum in a remarkable manner, often without leaving any apparent trace.

It does not necessarily follow that all cases of the formation of an opening in the mesentery are due to appendicitis. Other inflammations may also give rise to the same result. It is noteworthy that most, if not all, of these mesenteric openings are found in the mesentery of the lower part of the ileum. This is the site of election for many inflammatory conditions of the bowel—tuberculosis, typhoid fever, as well as many non-specific conditions.

The essential conclusion is that openings in the mesentery through which bowel may herniate may be the result of inflammatory damage to the mesentery—thrombosis of vessels, fibrosis, and atrophy* of part of the tissue—and the possibilities of such an origin should be thoroughly explored before a slit in the mesentery is regarded as an hereditary defect.

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* Since writing the above I observe that Barnard (*Contributions to Abdominal Surgery*, 1910, 207) includes atrophy as one of the causes of slits in the mesentery.

DYSCHONDROPLASIA (OLLIER'S DISEASE): WITH REPORT OF A CASE

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INTRODUCTION

THE disease which forms the subject of this communication has been given a variety of names. The title here chosen is that given by Ollier (1899), who appears to have been the first to recognize it. Recently there has been a tendency to regard all congenital lesions of the growing ends of bone as being manifestations of the same primary defect. There is, however, only the most superficial evidence that this is the case, and such a view seems only to have arisen because knowledge of these disorders is largely limited to that obtained by radiographic methods. In particular, hereditary deforming chondrodysplasia, diaphysial aclasis or hereditary multiple exostoses, and Ollier's dyschondroplasia are often regarded as the same disease (Coon, 1911; Ashhurst, 1916; Ehrenfried, 1917; Voorhoeve, 1924), but the grounds for this claim are nowhere clearly stated. The view seems to have arisen because in both conditions there may be abnormal areas of cartilage, exostoses, and broadening of the metaphyses, but it only requires a careful examination of radiograms to distinguish a number of points of difference. In diaphysial aclasis hereditary transmission is a very striking feature. In Ollier's disease there is little if any evidence of this. Until knowledge is further advanced, it is wiser to maintain the distinction between these two conditions and not refer indiscriminately to the whole group as the chondrodysplasias. Admittedly there is a number of cases (Voorhoeve, 1924; Dahl, 1930) which is intermediate and cannot at present be placed in any category.

By 'Ollier's dyschondroplasia' we understand a disease of the growing ends of bone in which the normal ossification of cartilage fails to take place, so that, as the bone increases in length, there remain in the diaphyses areas of cartilage which do not ossify. The process is not primarily one of tumour formation, although in some cases, particularly in the long bones of the hands and feet, there may be a hyperplasia of cartilage. That the pale areas shown in radiograms are really cartilage has been amply confirmed by histological examination both in our own case and those of Köhler (1905), S. Johansson (1916), C. Johannessen (1923), Cole (1926), Cleveland (1928), and Sacerdote (1931).

Though the disease shows a tendency to be unilateral, the case which Ollier originally described was not strictly unilateral, since both hands were affected. Some cases have had only one bone or one limb affected, some have been unilateral, some almost entirely unilateral, and some bilateral. They have all had a similar clinical course and pathological findings. It has been found impracticable

to make a complete list of the bilateral cases because they have been published under widely different names. The search would cover some 4000 records of cases of congenital bone 'tumours'. There is appended, however, a list of 29 unilateral and 10 almost entirely unilateral cases which can be accepted as dyschondroplasia. There is reason to believe that the bilateral cases would not exceed this number. Except where otherwise stated in the bibliography reference has been made to the original articles. Such reference has led us to omit as irrelevant several cases appearing in the lists set out by other authors.

PUBLISHED CASES OF OLLIER'S DISEASE

A.—Distribution Strictly Unilateral.		*B.—Distribution Almost Entirely Unilateral.*
Adams	Jansen, J. W. F.	Cameron and Trethowan
Anschütz	Jansen, M. (2 cases)	Coon
Bentzon	Johannessen, C.	Fairbank
Boinet and Stephan	Johansson, S.	Flotow
Bojesen	Köhler	Fragenheim
Brockman	Kummer	Hackenbrock
Bromer and Rutherford	Lindstrom	Nové-Josserand
Burchard (2 cases)	Richard and Dupuis	Ollier (2 cases)
Cleveland	Sacerdote and Bonomini	Wittek
Cole	Thomason	
Flotow (2 cases)	Valentin	
Hessenthaler	Weber	
Huber and Advenier	Weiss	

ETIOLOGY

The etiology of Ollier's dyschondroplasia is, of course, unknown. The curious distribution of the lesions at the ends of the long bones suggested to Bentzon (1924) that the 'stripes' of cartilage followed the course of the branches of the nutrient artery. He injected the nutrient arteries of normal bones and found that such was indeed the case. From this he argued that probably the sympathetic nervous system was at fault. He then conducted a series of experiments on rabbits in which he destroyed part of the sympathetic chain by the injection of alcohol. Out of 27 rabbits successfully treated, 1 showed, in radiograms taken a month later, changes in one of the phalanges which resembled those in the phalanges in dyschondroplasia. However, histological examination in another four months revealed in these areas no cartilage. There was a considerable enlargement of the marrow cavity, and the cortex was of a coarser structure than that of the normal bone.

On the basis of these observations Bentzon argues that "Ollier's disease may be interpreted as the typical reaction of the bones against an active hyperæmia of the bone tissue, arising owing to anomalies in the vegetative nervous system". It seems to us, however, that the evidence is not sufficient to warrant the assumption of so unusual a departure from the habitual reaction of bone to hyperæmia. We do not mean that we feel the sympathetic nervous system can have no relation to the disease, but that it cannot cause it merely by producing hyperæmia. It is conceivable that it may exert in some other manner a direct influence on the metabolism of bone or cartilage.

In this connection there is another point of interest. In six of the cases of unilateral dyschondroplasia there has been a marked facial asymmetry (Bojesen, 1914; S. Johansson, 1916; C. Johannessen, 1923; Bentzon, 1924; J. W. F. Jansen, 1925; and Hessenthaler, 1929).

CASE REPORT

HISTORY.—R. J., male, aged 7 years (L. H. Reg. No. 31622/1932). He was born in London, the first child of Jewish parents, the only other pregnancy in the mother having been terminated by Cæsarean section because of heart disease. There was no consanguinity either in the parents or in the grandparents. At the age of 18 months he began to limp on the right leg, and was taken to a hospital for radiograms of bones. The father was told that there was 1½ in. shortening of the right femur, and that radiograms showed disease of the head and upper part of the shaft of the right femur. Osteitis fibrosa cystica was suspected. Radiograms revealed changes in other bones on the right side of the body. On March 26, 1931, a portion of the lower end of the right tibia was excised for histological section. No family history of bone disease was obtained (fifteen members of three generations on both sides of the family were questioned).

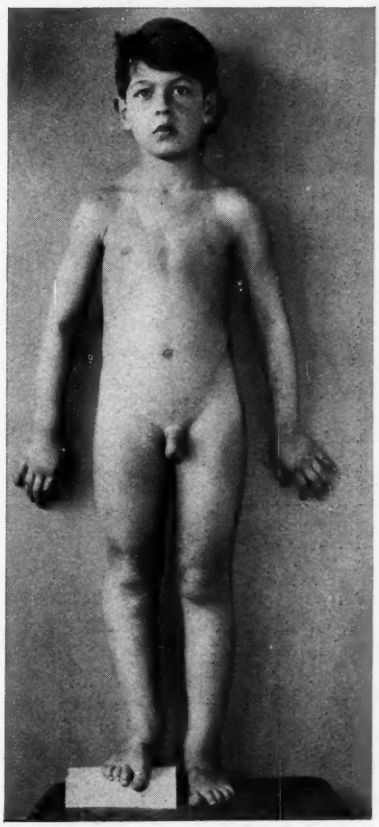

FIG. 356.—Photograph showing two inches of shortening in right lower limb. Upper limbs, thorax, spine, and skull normal. No facial asymmetry.

ON EXAMINATION.—Well-nourished boy, of normal mental development. Weight 3 st. 9 lb. Height 3 ft. 9 in. Mucous membranes normal colour, sclerotics white. Teeth: a few carious molars; upper central incisors and lower central and lateral incisors show serrated margins; no wedge-shaped teeth. Pupils equal, circular, react to light and on accommodation. Ocular movements full. Fundi normal. No abnormality in the cranial nerves, or elsewhere in nervous system. Pulse regular, 70. Heart and lungs normal. Blood-pressure 110/75 mm. of mercury. Abdomen normal. No facial asymmetry. Index fingers, tarsus, and carpus on both sides normal. Skull, spine, thorax, and both upper limbs normal. Right femur is shorter than left, with an outward bend (*Fig.* 356). Measurements: anterior superior iliac spine to internal malleolus, 22 in. right, 24 in. left. Anterior superior iliac spine to top of patella, 11 in. right, 12½ in. left. Bryant's triangle measurements, 1½ in. right, 2 in. left; that is, there is ½ in. deficiency in neck of femur, indicating coxa vara. Lower border of patella to internal malleolus, 9 in. right, 9½ in. left. Sternoclavicular joint to bend of wrist, 18½ in. right, 18½ in. left. Limitation of abduction with increased adduction in right hip. Rotation tests normal. Slight increased mobility in right ankle-joint. Both knee-joints are loose. Radiograms: skull, spine, ribs, and all bones on left side of body normal. Lesions seen in the following bones on *right* side of body—humerus, radius, metacarpals, phalanges of hands, ilium, ischium, pubis, femur, tibia, fibula, metatarsals, and phalanges of foot (*Figs.* 358–362). The most severe changes seen in the lower half of the femur, and upper third of the tibia: dense longitudinal bony trabeculæ with small, pale, mottled areas and scattered dense, punctate spots. The whole pattern of the spongiosa is altered, and the corticalis is in some places thin and expanded. Upper end of femur, lower end of tibia, upper ends of humerus, metatarsals, metacarpals, and phalanges show similar but less marked changes. The largest pale areas measure 1·5 by 0·8 cm., and the smallest 0·1 cm. across. The crest of the ilium shows pale fan-like striations extending in from the periphery. Controlled radiograms showed that outside these areas the shadows of all bones examined were of normal density. Blood chemistry: serum calcium 10·5 mgrm. per 100 c.c., plasma phosphorus 3·6 mgrm. per 100 c.c., plasma phosphatase 0·335 mgrm. Blood-count: red cells 5,700,000 per c.mm., hæmoglobin 96 per cent, colour index 0·84,

white cells 10,000 per c.mm., reticulocytes 0·6 per cent. Differential count normal. Urine normal; Bence-Jones protein not detected. Stools: pale brown, total fat 4·2 per cent of dried fæces. On a known low calcium intake (0·39 grm.), the calcium output in the urine (0·13 grm.) and the fæces (0·24 grm.) was normal.

HISTOLOGICAL REPORT (Professor H. M. Turnbull).—Tissue removed from lower end of right tibia, received from the Bland-Sutton Institute of Pathology, the Middlesex Hospital. I have examined the hæmatoxylin eosin and van Gieson sections. The bone has been broken in preparation, and it is difficult to be certain of the orientation. The corticalis contains a large piece of hyaline cartilage of irregular shape, upon which bone has been deposited in many places (*Fig.* 357). The cells are larger and more irregularly distributed than in normal epiphyseal cartilage. The cartilage is calcified in parts of its periphery. In such spots many of the cells are hypertrophic, but I cannot find the typical changes that are provisional for endochondral ossification. In parts of its periphery the cartilage passes directly into a zone of dense fibrous tissue. There appear to be other pieces of hyaline cartilage within the fibrous periosteum.

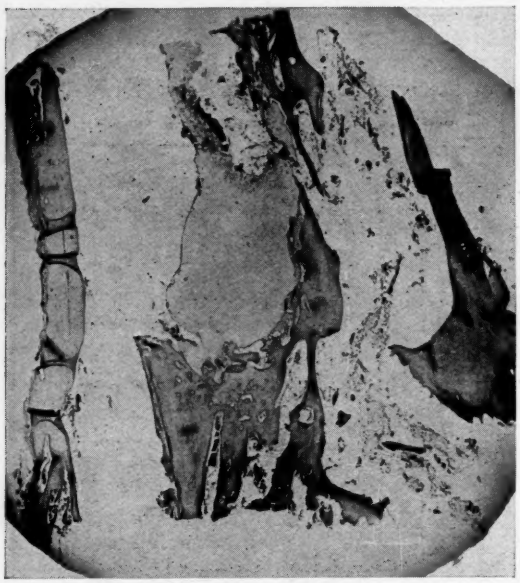

FIG. 357.—Photomicrograph of histological section of tissue removed from lower end of right tibia. The corticalis contains a large piece of hyaline cartilage of irregular shape upon which bone has been deposited in many places. (⅔ in. obj.)

Cartilage is formed in focal osteitis fibrosa, at any rate in young subjects. There is no trace, however, of osteitis fibrosa here. The inclusion within the corticalis of remnants of atypical epiphyseal cartilage is a characteristic of congenital chondrodysplasia. I have not, however, in that condition seen a fibrous zone upon parts of the surface of remnants, nor have I seen portions of cartilage within the fibrous periosteum as in this section. Otherwise, the section suggests congenital chondrodysplasia to me. There is considerable porosis of the corticalis but no evidence of rickets or malacia.

RADIOLOGICAL APPEARANCES

In every difficult case of disease of the ends of the long bones or of the bones of the hand or foot, radiograms of the entire skeleton must be taken, otherwise a case of dyschondroplasia may be overlooked. The disease may be limited to one bone only, to one limb, to one side of the body, or almost every bone may be affected. It is probable that the spine and the carpal and tarsal bones escape entirely, whilst the ribs, sternum, and skull are involved only very rarely.

The long bones—namely, humerus, radius, ulna, femur, tibia, and fibula—are those in which the typical appearances of dyschondroplasia are to be seen. The more rapidly growing end of a bone is that most commonly affected, but the opposite end may be involved too. The centre of the shaft remains normal except in very severe cases. The appearance of an affected region varies as the disease progresses. The changes seen in the early stages are well shown in the lower end of the femur and the upper end of the tibia of our case (*see Figs.* 359, 360). There is a translucent pyramidal area with its apex at the nutrient foramen and

its base resting on the epiphyseal line. This area is divided up by septa about 0·5 to 1·0 cm. apart, running approximately in the long axis of the bone. The lateral view may show the depth of involvement to be much less than might be expected from the antero-posterior pictures (C. Johannessen, 1923; Bentzon, 1924). Such translucent areas may extend over the whole width of the bone or be limited to any part of it (Burchard, 1913). At times there is only one narrow stripe in the middle of the bone.

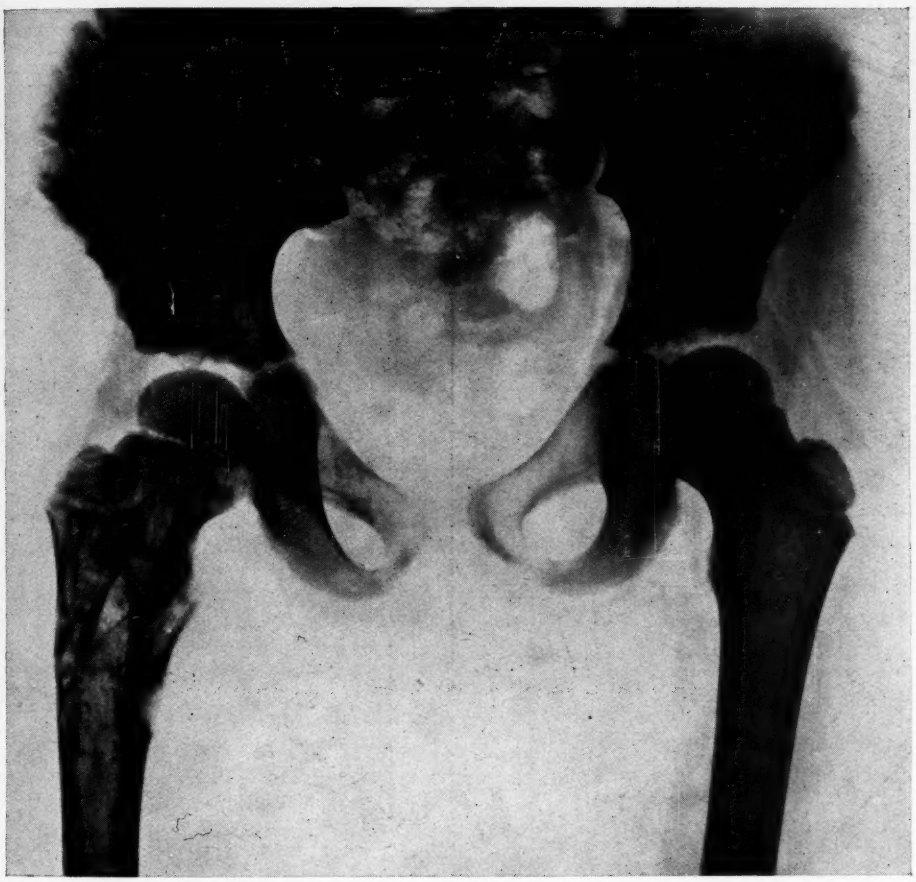

FIG. 358.—Radiogram of pelvis. Fan-like striation in crest of right ilium. Pale striation, mottled areas, and scattered dense punctate spots in head and neck of right femur. Bones on left side normal.

The affected ends of the diaphysis may have an outline of normal size and shape, or alternatively they may be broadened. This broadening tends to be a fusiform enlargement (Cleveland, 1928; Ballin, 1933), but in rarer cases it resembles that in diaphysial aclasis (Cole, 1926). Similarly small exostoses may occur near the ends of the diaphysis, but they are irregular in shape (Kummer, 1918; Weber, 1920; Weiss, 1923) and have a core rather than a shell of cartilage.

At the upper end of the femur the region usually affected earliest is the lesser trochanter (*see Fig.* 358), and progressive involvement takes place across

the bone to the great trochanter (Bojesen, 1914; C. Johannessen, 1923; Lindstrom, 1924). Sacerdote described a case in 1931 where only the great trochanter was involved.

The upper end of the humerus is affected above the level of the insertion of the deltoid, but the striping is not here well marked. When the lower end of the radius is involved it usually shows some shortening and forward bowing, at times resembling that to be seen in diaphysial aclasis or in Madelung's deformity. The lower end of the humerus and the bones of the forearm of our case, however, are practically normal.

FIG. 359.—Radiogram of femora. Right femur two inches shorter than left. Pale and dense streaks, pale mottled areas, and dark punctate spots in lower end of right femur. Extensive alteration in pattern of corticalis and spongiosa. Left femur normal.

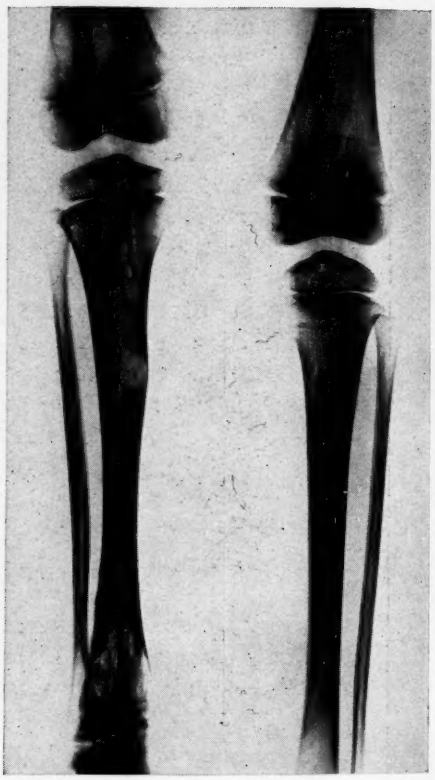

FIG. 360.—Radiogram of tibiæ. Extensive areas showing pale striped and mottled areas at both ends of right tibia and near centre of shaft. Many dark punctate spots. Lines of cessation of growth are seen near both knee-joints, but the left tibia is otherwise normal.

In the ilium the distribution of the cartilaginous areas is most striking. Only the periphery of the ilium, usually over a fan-shaped area in the middle of the bone, is affected, and the striping is very marked (*see Fig.* 358). In a few cases the whole of the flat portion of the bone is involved (Brockman, 1931; Kochs, 1932).

The ischium and the pubes, especially near the ischial tuberosity, may be affected, giving rise in the radiograms to a fluffy appearance due to the presence of many small rounded islands of cartilage. There is never any striping here.

The phalanges, the metatarsals, and the metacarpals differ from the long bones in that, as a rule, they contain only simple enchondromata which can in no way be distinguished from the isolated enchondromata occurring apart from dyschondroplasia. They may occur in any part of the diaphysis of the bone and grow to a considerable size. They are usually described as being of two types, central or medullary, and subperiosteal. In the absence of stereoscopic radiograms it is difficult to differentiate these types. Isolated enchondromata may also occur in any part of the shaft of the long bones. They are not common and cannot be regarded as typical of the condition. Occasionally, however, striping similar to that found in the long bones is seen in the metacarpals,

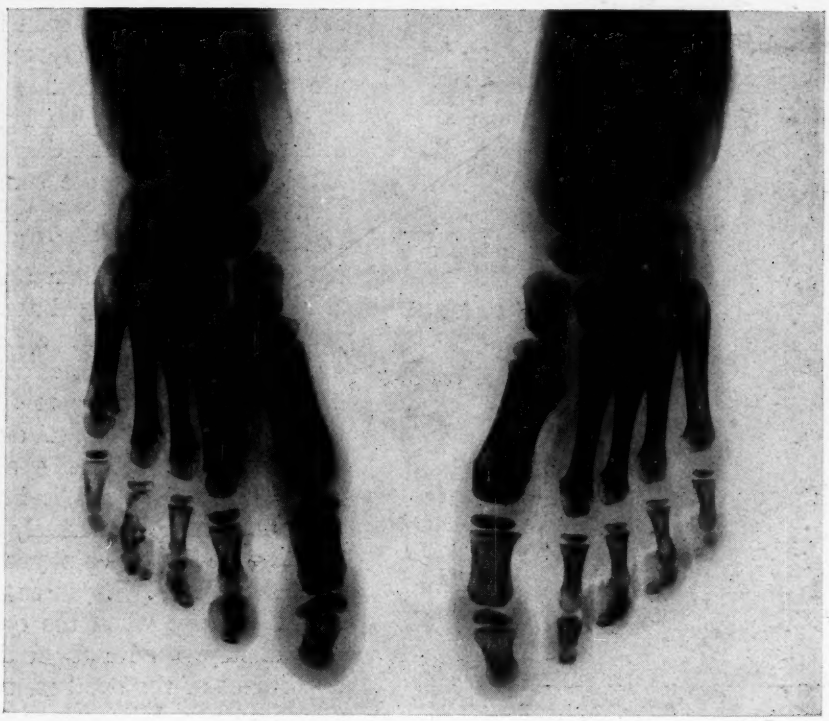

FIG. 361.—Radiogram of feet. Metatarsals and phalanges of right foot show small, pale, mottled areas and a few dense punctate spots. Left foot normal.

metatarsals, and phalanges. This occurred in the case of Huber and Advenier (1929), and is seen also in our case. *Fig.* 362 shows the disease affecting the growing ends of some of the phalanges and metacarpals; in the second phalanx of the ring finger striping can be distinctly seen—in strong contrast is the sharply circumscribed, clear area in the middle of the second phalanx of the index finger, which resembles the enchondromata usually to be found in the fingers.

As the child grows older, the typical striped appearance disappears and is replaced by a speckling due to islands of dense calcification. As our own case is too young to show this well, we reproduce by courtesy of Mr. A. Rocyn-Jones the right femur of a girl now aged 21 years who is suffering from dyschondroplasia and in whom nearly every bone is affected. A radiogram (*Fig.* 363) taken

at the age of 3 shows the typical appearance described above for early cases. At the age of 15 marked speckling (*Fig.* 364) has replaced the earlier appearances. The case is only introduced here to show the appearance of dyschondroplasia at a later age. The same appearance is well shown in published cases (Boinet and Stephan, 1903; Cole, 1926; Cleveland, 1928; Hessenthaler, 1929). At a later stage still there is a tendency for the structure of the bone to approach more closely to the normal, although it is doubtful if it ever becomes completely so. That speckling does not always occur, however, can be seen in the case of a woman aged 38 published by Weiss (1923). Here the striping has spread into the epiphysis, which can no longer be distinguished from the diaphysis.

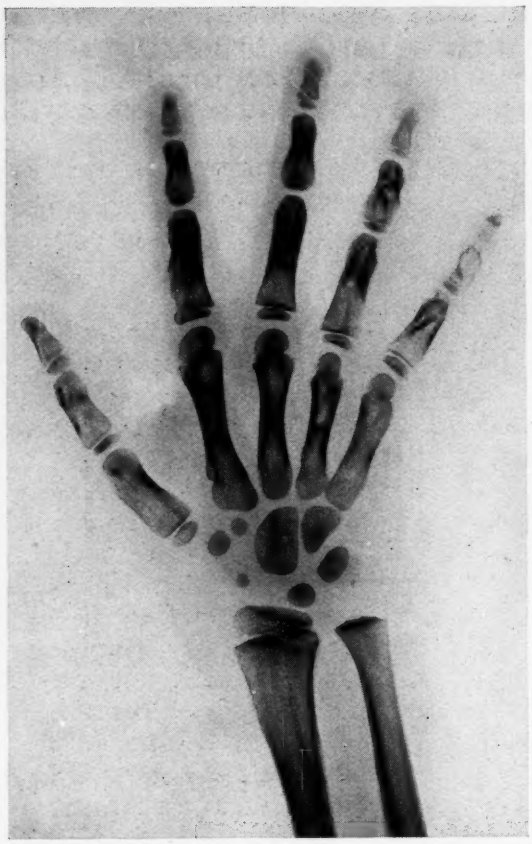

FIG. 362.—Radiogram of right hand. Right radius and many phalanges and metacarpals show pale mottled areas, sometimes with dense punctate spots.

The epiphyses are completely unaffected at birth. The exact age of their involvement varies in different cases. They seldom show the striping of the long bones, but present the speckled appearance due to irregularities of calcification. This is just beginning to show in the femoral epiphysis of our case (*see Fig.* 359). If only a small strip of the diaphysis is involved, then only an approximately corresponding width of epiphysis seems to suffer (J. W. F. Jansen, 1925). After the age when the epiphysis and diaphysis normally unite the appearance of the two becomes uniform and shows irregular speckling (Cole, 1926).

DIFFERENTIAL DIAGNOSIS

Dyschondroplasia and the conditions which resemble it are rare. Since neither the physical nor the biochemical findings serve to identify the disease, the diagnosis largely depends upon examination of radiograms. In an early clear-cut case the picture is so typical that it should present no difficulty. Nevertheless, confusion not infrequently occurs, even in obvious cases. Thus Ballin (1933) writing on 'parathyroidism' describes the radiograms in what is clearly a well-marked case of dyschondroplasia as showing "the simultaneous existence of osteopoicilia and osteitis fibrosa cystica".

In cases which are unilateral or nearly so, no difficulty is likely to arise. Unilateral diaphysial aclasis does occur. Stocks and Barrington (1925) found

evidence of this in 11 per cent of 446 cases, but in this series radiograms of the whole skeleton were not available. We know of only one case of multifocal osteitis fibrosa where the distribution was unilateral (Fairbank, 1933).

The positive diagnosis of dyschondroplasia is made on three main points :—

1. The onset is in early childhood.

2. Radiograms show changes limited to the ends of the long bones. There is striping of rarefied areas. The epiphyses are involved only secondarily. Speckling appears in the affected metaphyses and epiphyses as growth proceeds.

3. A portion of tissue corresponding to a pale area in a radiogram is found, when excised and examined histologically, to consist of cartilage.

Diaphysial Aclasis (Hereditary Multiple Exostoses).—This is characterized by four main features which differentiate it from dyschondroplasia.

FIG. 363.—Radiogram of lower limb in a child (aged 3) suffering from dyschondroplasia. Patient is now 21 years of age and nearly every bone is affected. Both lower end of femur and upper end of tibia show characteristic translucent areas divided up by septa running approximately in the long axis of the bone.

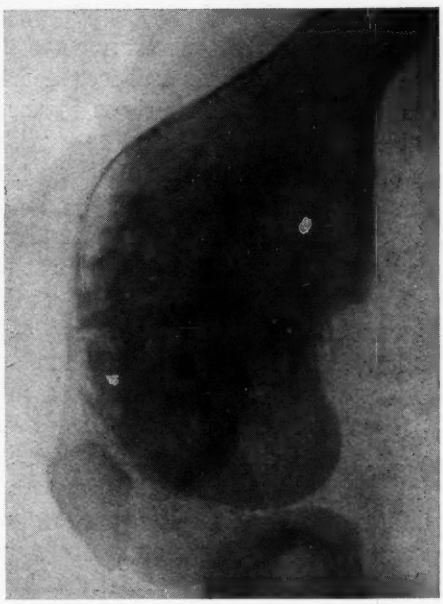

FIG. 364.—Radiogram of lower end of femur taken twelve years later than that in *Fig.* 363, the patient being 15 years of age. Speckling due to islands of dense calcification has replaced the striping found at the earlier age.

1. Heredity is a very striking feature. Stocks and Barrington (1925) found that in 1124 recorded cases 727 or 64·7 per cent gave a definite history of the disorder occurring among antecedents or relatives.

2. The presence of ossifying ecchondromata (exostoses) is almost invariable. They are usually pedunculated, may arise anywhere along the length of the bone, point away from the end of the bone, and are well defined and clear-cut. In dyschondroplasia they arise near the epiphyses, point in any direction, are rough and irregular, and never reach any great size (Ehrenfried, 1917).

3. Broadening of the metaphysis is essential to the diagnosis of diaphysial aclasis. It is a fairly regular process, beginning abruptly with a sudden trumpeting of the shaft and with sides approximately parallel. In dyschondroplasia the metaphysis is often normal in size and shape but it may be expanded in a fusiform manner. Only very occasionally does it approach in appearance the uniform trumpeting described above (Keith, 1920).

4. In diaphysial aclasis, although there may be enchondromata present, there is fairly regular ossification giving a homogeneous structure to the bone. In dyschondroplasia in the early stages there is regular arrangement of cartilage and in the later stages stippling of the epiphyses.

There are, of course, a few cases which it is difficult to place in any group (Voorhoeve, 1924; Mauclaire, 1926; Dahl, 1930), but this is probably because they have only been observed in one stage of their progress. If they could be watched growing up from infancy there would be less difficulty.

Multiple Enchondromatosis.—This is a condition affecting the long bones of the hands and feet. The radiographic appearances are identical with those seen in the hands and feet in dyschondroplasia. It is impossible to say whether or not the former disease is a localized form of the latter. It is equally impossible to explain why it is that the hands and feet in cases of dyschondroplasia so often show changes which are different from those in the rest of the skeleton. There are rare cases (Steudel, 1892; Fragenheim, 1911; Hackenbrock, 1922) in which massive enchondromata occur in the hands and feet, giving rise to hideous deformity. This probably occurs only in association with dyschondroplasia. It is difficult to classify accurately those cases which are published under the title "systematized multiple enchondromata", but they seem for the most part to be atypical cases of dyschondroplasia.

Voorhoeve's Disease.—The radiograms of bones show long fine parallel lines of increased density in the region of the metaphyses and some mottling of the epiphyses. The distribution is similar to that in dyschondroplasia, but the pale shadows of cartilaginous areas are missing (Voorhoeve, 1924).

Speckled Epiphyses.—The small bones of the hand and foot and the epiphyses of the long bones appear in radiograms as countless small black dots (Fairbank, 1927).

Osteopoikilosis.—X-rays show areas of excessive density scattered throughout the entire bone. These areas are usually a few millimetres in diameter, and may be rounded or elongated to a few centimetres in length, in which case the long axis is in the long axis of the bone (Albers-Schönberg, 1915; Ledoux-Lebard, 1917).

Generalized Osteitis Fibrosa (Hyperparathyroidism).—The diagnosis of this condition by no means depends only on radiograms. The patient may show generalized tenderness of bones, and there may be symptoms unrelated to the skeleton, such as vomiting, renal colic, or muscular hypotonia. The characteristic biochemical findings of hyperparathyroidism will be present—namely, a persistently high serum calcium and low plasma phosphorus. The output of calcium in the urine may reach six times the normal figure. Radiographic examination of the bones by the controlled method will show diminished density of the shadows of all bones affected. In addition to this generalized change, multiple pale cyst-like areas may be found anywhere in the skeleton, and in the case of the long bones there may be expansion of the corticalis (Mandl, 1929; Barr, Bulger, and Dixon, 1929; Wilder, 1929; Hunter and Turnbull, 1931; Gordon-Taylor and Wiles, 1932).

Focal Osteitis Fibrosa.—In cases of focal osteitis fibrosa with multiple foci a large number of bones in the body may be affected. In spite of this, the serum calcium, plasma phosphorus, and urinary calcium excretion remain normal (Hunter, 1930). There is no generalized rarefaction of the skeleton, many areas of bone being found which compare in density to the control. The distribution of the cystic areas is quite haphazard. The areas of bony rarefaction show irregular shapes. They are often limited by a line of increased density and they may expand the corticalis. In dyschondroplasia the pale shadows of cartilaginous areas are localized to the neighbourhood of the metaphyses.

Gaucher's Disease.—In 1922 Pick discovered a gross osseous form of this disease. He described cases with marked skeletal changes in the form of erosion of the corticalis, pathological fractures, and angular curvature of the spine. Junghagen in 1926 called attention to the use of radiograms of bones in the diagnosis of Gaucher's disease. In view of the obvious enlargement of the spleen and the changes in the blood, confusion with dyschondroplasia should not occur.

Xanthomatosis of Bones.—Xanthomatous deposits in the skull, especially in association with exophthalmos and diabetes insipidus, are now well known (Hand, 1893; Schüller, 1915; Christian, 1919). That the calvaria may escape, though other bones are extensively affected, has been shown recently by Snapper and Parisel (1933). In some cases increase in the total cholesterol content of the blood confirms the diagnosis. Histological examination of a portion of excised bone shows the characteristic foam cells of lipoid-granulomatosis.

Lymphangioma of Bone.—There is one remarkable case (Wrede, 1911) which might well have been mistaken for dyschondroplasia on radiographic evidence alone. Pale shadows were observed in the upper ends of the tibia and fibula of a girl aged 6 years. Biopsy was refused, but the appearance and history of the child suggest that the bone lesions may have been lymphangiomata.

COURSE

The actual age of onset usually is not known, but some abnormality is often first noticed between the first and second years of life, when, as a rule, one limb is found to be shorter than its fellow. The difference in length becomes progressively greater as growth proceeds. By about six years of age bending of the limbs or enlargement of one or more fingers may be apparent. Deformity may be due to weight-bearing causing bending of the bone, to the irregular rate of growth in those cases in which only a portion of the width of the diaphysis is affected, or to the different rate of growth where only one of the paired bones is affected.

At the earliest stage the diaphysis only is involved and the epiphyses are unaffected. After about five years of age the epiphyses may become involved. The radiographic appearances suggest that the disease spreads from the diaphysis to the epiphysis and it may well be that this spread bears some relation to a change in blood-supply. However, we have at present very little exact knowledge as to the details of the blood-supply to the epiphyses at different ages.

As the patient gets older, areas of calcification appear in the affected areas, giving to radiograms a very typical appearance. This change probably occurs round small patches of degeneration in the cartilage. The age at which it takes place is subject to great variation but it does not usually commence until after six

years and it may be delayed much longer. By the time the epiphyses would normally have united to the diaphysis the two present a uniform picture and appear to consist of cartilage studded more or less thickly with calcified areas a few millimetres across. It is probable that the bones never become completely normal, but some of the radiograms of the older cases show an approach to the normal structure; the 'speckling' becomes much fainter and some cancellous structure appears.

PROGNOSIS

The majority of cases reported in the literature are children, and no mention of the same cases appears subsequently. There are, however, several cases reported in their early twenties as alive and well, and the patient described by Weiss (1923) reached the age of 38 before attending a clinic, but he does not say of what she then complained. The case reported by Boinet and Stephan (1903) died at the age of 35, apparently from a sarcoma, but there had been several fractures and also some operative interference. The patient described by Nehrkorn (1898) was probably a case of dyschondroplasia and he died of a sarcoma of the thigh at the age of 49 years. In the case reported by Lea (1929) a frontal glioma appeared at the age of 28 years. The patient described by Speiser (1925) died of anæmia at the age of $4\frac{1}{2}$ years. The patient reported by Nasse (1895) developed massive tumours of the fingers and thigh, and eventually was reported by Fragenheim (1911) as having died following a disarticulation of the hip performed for the relief of pain.

The actual incidence of sarcoma cannot be determined, but the prognosis apart from this seems by no means bad. Most patients seem to reach adult life, when their symptoms are mainly those of their deformities and sometimes of a secondary arthritis.

TREATMENT

Treatment is concerned with the prevention and relief of deformities and proceeds along the usual orthopædic lines. Osteotomy has been performed in at least six cases (Köhler, 1905; Thiemann, 1910; Hackenbrock, 1922; J. W. F. Jansen, 1925; Cleveland, 1928; Flotow, 1929) and has met with no untoward results. Fractures are of fairly common occurrence and, like the osteotomies (Köhler, 1905), appear to unite well.

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COLOSTOMY

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THE chief value of colostomy as a palliative operation in malignant disease of the rectum is afforded by the relief of obstruction, and to a varying degree by the relief of important and troublesome symptoms such as diarrhœa, tenesmus, pain, bleeding, and discharge. The improvement in these symptoms varies greatly with different patients, as much owing to differences in temperament and management as to differences in the types of primary tumour (scirrhous, colloid, ulcerating, or vascular), their situation (upper, middle, or lower third of the rectum), and the extent of extra-rectal spread.

In *some* cases, such as those with obstruction, recto-vaginal, recto-vesical, or vesico-colic fistula, the relief given by a colostomy is undeniable; in *most* cases after colostomy there is at first, for a varying number of months until a late stage of the disease is reached, a definite improvement not only locally, but also in the patient's general condition; this is to be accounted for by the ability to take a more normal diet, by proper bowel evacuations, relief of rectal irritability, and more regular sleep. For these reasons colostomy is rightly regarded as a beneficent operation for the relief of inoperable rectal cancer.

The benefits conferred by a colostomy are most appreciable if the operation is done at a stage when the patients are still capable of some general improvement, and have time and courage to adapt themselves to a colostomy life. If the operation is not done until a late stage of the disease, the operative risks are greatly increased: the patients are often in a poor state of health, under-nourished, dehydrated, and worn out by loss of sleep from diarrhœa, tenesmus, or pain. Accompanying conditions such as dental sepsis, chronic bronchitis, and urinary infection, retention, or failure, are often present and aggravate the risk of an abdominal operation.

The following study concerns a series of 500 cases of palliative colostomy for inoperable rectal cancer which have been admitted into St. Mark's Hospital in the course of the last twenty-four years. We shall show that the operation mortality of colostomy in these advanced cases is considerably greater than that of colostomy in a parallel series of 470 operable cases in which an excision of the rectum was either planned or carried out as a second-stage operation. The added risks of palliative colostomy when done in advanced age or in the late stages of obstruction will be shown, but even so we believe that the operation is justified by the relief of obstruction and other symptoms, and in certain cases by a notable prolongation of life.

It is difficult, however, to assess in a satisfactory manner the value of colostomy in a series of cases. The relief of symptoms and the prevention of obstruction

cannot be measured in words or tables. The definite facts which can be recorded are concerned chiefly with: (1) Operation mortality in relation to age, sex, and stage of the disease; (2) The causes of operative deaths, with suggestions for avoiding certain immediate complications; (3) The duration of life after colostomy; (4) Late complications and sequelæ connected with colostomy; (5) Operative technique of left iliac colostomy.

OPERATION MORTALITY AND IMMEDIATE POST-OPERATIVE COMPLICATIONS

The following statistics and discussion of operative mortality after colostomy and immediate post-operative complications are compiled principally from 500 cases of palliative colostomy for inoperable cancer of the rectum and pelvic colon, in which series 67 deaths occurred (13·4 per cent).

Table I.—Operative Mortality of Colostomy in Relation to Age and Sex

Age Incidence in Years	Males			Females		
	No. Operated Upon	No. of Operative Deaths	Per Cent	No. Operated Upon	No. of Operative Deaths	Per Cent
20–29	7	1	–	4	0	–
30–39	12	0	–	11	0	–
40–49	37	7	19	13	1	7·7
50–59	113	13	11·5	39	5	12·5
60–69	151	15	10	47	12	25
70–79	53	10	19	12	3	25
80–89	1	0	–	–	–	–
Total ..	374	46	12	126	21	17

In 236 cases under 60 years of age there were 27 operative deaths = 11·4 per cent.
In 198 cases between 60 and 69 years of age there were 27 operative deaths = 13·6 per cent.
In 66 cases of 70 years and over there were 13 operative deaths = 20 per cent.

A consideration of *Table I* shows the following points:—

1. The preponderance of males over females in the proportion of 3 to 1.

2. The higher proportion of inoperable carcinoma in females under 40 years of age (12 per cent) compared with males under 40 years of age (5 per cent).

3. In males 14 per cent were over 70 years of age, but in females only 9 per cent.

4. The total mortality as shown is 13·4 per cent, with the higher mortality of 17 per cent in females compared with 12 per cent in males. The female deaths are seen to rise steadily in each decade from 40 onwards, but in males the mortality has been irregular: it was at its maximum in the decade 40–49 and in patients over 70; in the former group there occurred 4 deaths from peritonitis which will be further considered in the following section, and in the latter group the principal causes of death have been pulmonary or cardiac complications.

Among a separate series of 470 cases which were assessed as "operable" there occurred 12 deaths (2·5 per cent) which were directly attributable to the colostomy.

These may now be added to the 67 deaths recorded in *Table I*, giving thus a total of 79 operative deaths from colostomy, an analysis of which is shown in *Table II*. We wish to draw particular attention to the deaths from peritonitis and paralytic obstruction.

Table II.—Causes of 79 Operative Deaths in 970 Cases of Colostomy, 1910–33

Cause of Death	Total Number of Deaths due to this Cause	Males	Females
Heart failure	11	7	4
Pulmonary complications	11	8	3
Pulmonary embolism	2	1	1
Peritonitis	12	7	5
Paralytic ileus	9	6	3
Mechanical obstruction	5	4	1
Toxæmia from pre-operative obstruction	4	3	1
Prolapse of small intestine	9	7	2
Uræmia	6	4	2
Cachexia	5	2	3
Miscellaneous	5	4	1
Total	79	53	26

Cardiovascular and Pulmonary Complications.—This forms the largest group, with a total of 24 deaths. There were 11 deaths from cardiac failure, the average age of these cases being 66 years, at an average time of five days after operation. In one case the rectal carcinoma had been assessed as operable, but the patient collapsed suddenly on the ninth day and died in a few minutes; a post-mortem examination revealed atheroma of the coronary arteries, with occlusion of one branch; the remaining patients had inoperable growths and died from myocardial or coronary disease. There were 10 deaths from bronchitis or broncho-pneumonia at an average age of 64 years, and an average time of ten days after operation; and 1 death from acute pulmonary œdema within twenty-four hours of operation in a young man of 25 with an advanced obstructing carcinoma in the upper third of the rectum. There were 2 deaths from pulmonary embolism—a male, aged 64, on the fifth day, and a female, aged 62, on the fourth day: in both cases secondary deposits were proved to be present in the liver.

Peritonitis.—The 12 cases that died from peritonitis after colostomy form an instructive group; in 10 of these cases the presence of peritonitis was proved either at a secondary operation or post mortem, and the causes of the infection may be classified as follows:—

1. In 3 cases the peritonitis was secondary to suppuration in the abdominal wall round the colostomy, and death took place on the thirteenth, thirteenth, and fourteenth day after operation respectively. In each case the 'delayed' method of opening the colostomy forty-eight hours after operation had been adopted.

2. In 5 cases abdominal exploration of the rectal growth must be accounted the exciting cause of peritonitis: the following are the significant details of these cases:—

Case 1.—E. W., a gardener, aged 49, with an inoperable carcinoma at the recto-sigmoid junction which had been explored at another hospital a few weeks previously. Laparotomy revealed a large fixed mass in the lower pelvic colon with dense surrounding adhesions, and a left iliac colostomy was established. Peritonitis with obstruction supervened, and jejunostomy with drainage of the pelvis was done on the fourth day, but the patient died next day.

Case 2.—T. M., a porter, aged 45, with a small mobile carcinoma at 15 cm. from the anus. The tumour was explored through a paramedian incision and left iliac colostomy was performed. On the second day the patient had a rapid pulse and moderate abdominal distension; this became worse, and a cæcostomy was done, but the patient died from peritonitis on the fourth day. At the post-mortem no definite focus of infection was found.

Case 3.—Mrs. A. E., aged 58, with a large fungating carcinoma in the upper third of the rectum. An exploratory laparotomy and a left iliac colostomy was done; on the second day the abdomen became distended; small amounts of flatus were passed per colostomy, but a condition of partial obstruction developed. On the sixth day, under spinal anæsthesia, a further laparotomy was done and revealed a low-grade peritonitis, many coils of small gut being adherent, and flakes of lymph present. Death took place the same evening, and at the post-mortem a general peritonitis was confirmed, without any definite focus of infection being found. Secondary deposits were present in the diaphragm and right lung.

Case 4.—E. C., a carman, aged 52, with an extensive carcinoma in the middle third of the rectum: there was a previous history of dysentery. A paramedian laparotomy was done, and some adhesions between the growth and the bladder were broken down with a finger before establishing a colostomy. On the third day vomiting and hiccup began, and the patient rapidly failed and died on the same day. A post-mortem examination showed pelvic peritonitis with the small intestine adherent in the pelvis where adhesions between the bladder and the rectum had been separated, and a small perforation into the rectum was demonstrated at this point.

Case 5.—J. R., a man, aged 63, with a constricting carcinoma at 12 cm. from the anus. Laparotomy confirmed the presence of a supraperitoneal growth, and an adherent loop of ileum was separated from the growth: a fistula into the ileum was then found to be present, and the affected loop was resected. A colostomy was then made and a Paul's tube tied in, but the patient died from peritonitis on the fourth post-operative day.

It will be noted that in the first three cases in this group no definite focus of the peritoneal infection was found: presumably it arose from handling the growth or mobilizing adhesions in the neighbourhood of the growth, and this experience indicates the extreme care and gentleness which should be exercised in exploring a carcinoma of the pelvic colon or upper rectum through an abdominal incision. If the growth is inoperable, there is no object in breaking down adhesions except to the minimum extent necessary for mobilizing the pelvic colon for a colostomy. The presence of diverticulitis of the pelvic colon in association with a carcinoma is a dangerous one which calls for special notice of the risk of breaking down adhesions and exposing septic areas.

3. In 2 cases peritonitis was caused by the opened colostomy slipping back into the abdominal cavity, in one case owing to the rod being inadvertently removed on the second day, and in the other case the rod ulcerated through the spur on the eighth day after operation, allowing the lower end to slip back into the pelvis.

4. In one case a fatal peritonitis resulted from a perforation of the colon a few inches proximal to the colostomy.

Case 6.—The patient, Miss M. C., aged 53, had a large inoperable rectal carcinoma. A colostomy was performed and was opened on the following day: colostomy wash-outs were then begun in order to relieve her distension. On the second evening after operation acute abdominal distension rapidly developed after an ox-bile enema had been given into

the colostomy, with severe griping pain and a pulse-rate of 156 per minute. She died on the third day after operation, and at the post-mortem a general peritonitis was found originating from a perforation of the descending colon 4 in. above the colostomy at the point where the bowel turned forwards from the posterior abdominal wall to the colostomy; at this point there was a small linear slit in the bowel wall about half an inch long.

It is believed that the perforation was caused by an injudicious attempt to pass a flatus tube round this 'corner' of the bowel, and point is attached to this theory in that this accident is known definitely to have caused the death of another patient not included in this series four days after an abdomino-perineal excision of the rectum: in this case a post-mortem examination revealed an exactly similar perforation which had undoubtedly been caused by a tube. The lesson which may be drawn from these cases is that under certain conditions a rectal tube may be dangerous for passing down a colostomy: in fat subjects the bowel is often thin-walled and friable, and a soft rubber catheter, about No. 16 in size, is the only kind which should be used for this purpose.

5. In one case operated upon in 1910 the pelvic colon was divided above an inoperable growth: the upper end was brought out as a terminal colostomy, the lower end being closed and dropped back. Symptoms of peritonitis began on the fourth day. Post mortem septic peritonitis due to leakage from the dropped-back colon was found to be present.

Paralytic Ileus.—In this group there were 9 patients, 6 males and 3 females, and all had symptoms of continued obstruction following the opening of the colostomy. These cases occurred at intervals from 1911 to 1933, and 4 of the cases were assessed as operable. In the 5 cases that have occurred since 1928 either post-mortem examination or a secondary operation has been performed, and we are satisfied that the condition was one of paralytic ileus involving the small intestine. Four previous cases have an identical history and have accordingly been placed in this group. General anæsthesia was used in all the cases but two, in which spinal anæsthesia was given.

The composite clinical picture in these cases is as follows: The colostomies were opened at an average time of approximately thirty-six hours after the operation, and the first symptoms and signs were those of slight abdominal discomfort and distension appearing from the second to the fourth day. Colostomy wash-outs were immediately commenced with relatively poor results, and abdominal distension gradually increased, being at times slightly reduced by wash-outs and finally failing to respond to any form of treatment. The usual hypodermic injections such as pituitrin and eserine were given in conjunction with various wash-outs, turpentine, ox-bile, and human bile, and also intravenous salines. Acetyl-choline was not used in any of the cases in this series as the majority occurred before this treatment was described. The following is a characteristic case:—

Case 7.—S. S., aged 55, a storekeeper, was admitted with an operable carcinoma in the lower third of the rectum. The patient was a thin, underfed subject. Examination of the heart revealed no abnormality, the blood-pressure was 175/125, and the blood-urea 67 mgrm. per 100 c.c. of blood. Five days after admission a left inguinal colostomy was performed under spinal anæsthesia; there was very little intraperitoneal manipulation. The colostomy was opened twenty-four hours after the operation; there was a slight escape of flatus and the abdomen appeared quiet and was not distended. The onset of the trouble was first noticed eighty hours after the operation, when the patient vomited an aperient which had been given, and complained of slight dull abdominal pain. On examination the abdomen

was found to be slightly distended in all quadrants, the pulse-rate was 106, there was some tendency to hiccup, and on auscultation the abdomen was silent. A flatus tube was passed into the upper colostomy opening and a slight amount of flatus obtained. Following this, 1 c.c. of pituitrin was given hypodermically, and twenty minutes later an ox-bile colostomy wash-out was given, a fæcal-coloured result being obtained with a slight amount of flatus. There was no further vomiting, the tongue was moist, the pulse remained above 100, and the patient was fairly comfortable except for slight abdominal discomfort due to the distension which was still present; the abdomen was still silent. At this stage 0·5 c.c. of pitressin was given three-hourly. Five to six hours later there had been no passage of flatus per colostomy, the pulse-rate was rising gradually, and the abdomen was still distended—slightly more so in the upper half; a Ryle's stomach tube was passed and 12 oz. of dark-brown acid contents withdrawn. This tube was kept *in situ*, and further stomach contents were withdrawn two-hourly. At the same time a continuous intravenous normal saline with 5 per cent glucose was given at the rate of 10 oz. per hour for the next seven hours, and then, twenty-two hours after the onset of symptoms, another ox-bile enema was given with a slightly fæcal and good flatus result. The pulse-rate had now risen to 130 per minute, the blood-pressure was 160/120, but the abdomen was less distended. A second operation was being considered at this time, but became inadvisable as shortly after this the patient became delirious and then comatose. The abdomen remained in a condition of silent distension and the pulse-rate slowly increased. The patient finally died approximately forty-eight hours after the onset of vomiting—that is, on the fifth day after the operation.

Laboratory tests showed the urinary chlorides to be greatly diminished and later absent, despite the administration of intravenous chlorides; the blood-urea rose steadily, suggesting a uræmic origin to the condition; however, the van Slyke clearance tests performed in this case clearly showed that despite the rising blood-urea the kidney function was unimpaired, and urine with a very high urea concentration continued to be excreted.

At the post-mortem a distended condition of the gastro-intestinal tract was found involving the stomach and the whole of the small intestine to within 2 ft. of the ileocæcal valve; at this point the distension gradually faded, and the remaining small gut distal to this point and the colon were found to be collapsed. There was no peritonitis or free fluid, and no adhesions were present in any part of the abdomen; there was no abnormality in any of the other organs.

In three other cases in which a post-mortem examination was performed, and in one other in which a second laparotomy was done, a similar condition with no evidence of peritonitis was found. Of the cases in this series, 3 were simple colostomy operations with relatively little intraperitoneal manipulation, and the remaining 6 had additional laparotomy wounds with more extensive abdominal manipulation. In 4 cases second operations were performed in a fruitless attempt to relieve the condition, though one case survived for nine days after a jejunostomy had been performed.

With regard to the causation, the only explanation which we have to offer is that this complication took place in patients with a poor bowel tone in which early distension took place after operation and *before the colostomy was opened.* We think it is correct to say that in the early cases in this series the abdominal wall was closed more loosely round the colon with the deliberate intention of allowing flatus to pass round the loop. In recent years the practice has been to make a rather tighter-fitting colostomy and to close the abdominal wall in layers as snugly as possible, so that until opened the bowel is actually obstructed.

This view is borne out by the figures, which show that 5 of these cases have occurred since 1928 and also that complications such as prolapse of omentum and small gut through the colostomy wound have in later years become much less frequent. We think that this obstructing type of colostomy may be a contributory cause, and for this reason we have made it our practice for the last two years

to open every colostomy on the table at the conclusion of the operation, and so far no case of paralytic ileus has followed this procedure.

Mechanical Obstruction.—This has accounted for 5 post-operative deaths; in 1 case a band was found post mortem obstructing the transverse colon, and in 2 cases the small intestine was proved to have become adherent and kinked, once at a transverse colostomy and once to the dropped-back colon in one of the early cases in this series (1913) where the bowel had been divided and a terminal colostomy established.

In 2 cases a knuckle of small intestine became strangulated through the foramen on the lateral aspect of a rectus colostomy.

Case 8.—G. G., a man, aged 53, with an operable anal carcinoma. A left rectus colostomy and perineal excision of the rectum was carried out in one stage. On the third post-operative day he became distended and began to vomit small intestinal contents; laparotomy revealed a small-gut obstruction due to a knuckle of the bowel entering from above downwards into the foramen on the outer side of the colostomy; the small intestine beyond this point was collapsed. The bowel was reduced, but the patient died four hours later. (*Fig.* 365.)

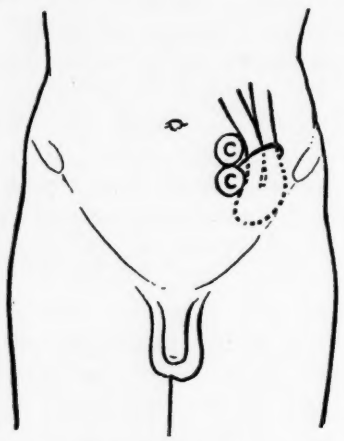

FIG. 365.—*Case* 8.

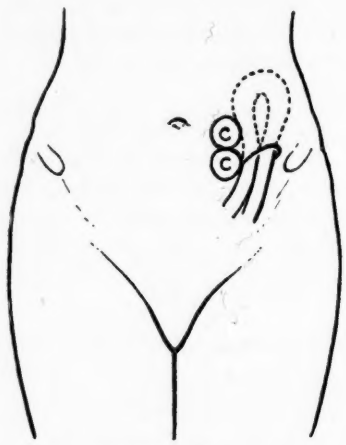

FIG. 366.—*Case* 9.

Case 9.—Mrs. E. S., aged 55, with an operable carcinoma in the ampulla of the rectum. A left rectus colostomy was established, and fourteen days later the rectum was excised by the perineal route. There was some post-operative vomiting and late on the second day after the excision operation the abdomen became distended and the patient rapidly failed. Post-mortem examination showed a small-gut obstruction 4 ft. from the duodenojejunal flexure, from below upwards round the colostomy. (*Fig.* 366.)

Since these cases were reported, together with 3 others in 1928 (Gabriel[1]), the expedient of closing the lateral space by suture when doing a colostomy has been generally adopted, and no further example of this type of obstruction has occurred in the immediate post-operative period in St. Mark's Hospital.

Toxæmia from Pre-operative Obstruction.—The added risks of colostomy when carried out in the late stages of obstruction are indicated by the cases in this series: 22 patients were admitted with marked abdominal distension, and of these 7 died after operation (32 per cent). Four of these died from toxæmia at an average of three days after operation, the remaining 3 deaths falling under other headings (pulmonary œdema, paralytic obstruction, and prolapse of the small intestine).

Prolapse of Small Intestine.—This complication has accounted for 9 fatalities in this series, and on analysis two points are at once apparent in regard to: (1) The incision used for the colostomy; and (2) The age of the patient.

1. In every case the colostomy was done through a left rectus incision, and the small intestine subsequently made its way through the upper and inner aspect of the wound. The increased risk of a rectus incision with direct underlying pressure from the small intestine is further shown by the other cases with this complication who recovered after operative reduction of the prolapsed bowel or omentum—namely, 3 cases of small intestinal prolapse (2 rectus colostomies, 1 left oblique), and 3 cases of prolapse of the great omentum (all rectus colostomies). There are thus altogether 15 cases of prolapse of the small intestine or omentum, of which only 1 was through a left oblique incision. The high mortality attached to prolapse of the small intestine is shown by the death-rate of 75 per cent (9 deaths out of 12).

2. That advanced age predisposes to this complication is shown by the fact that in 7 patients the age was between 60 and 77 years, with an average age of 67: in these cases the prolapse occurred as a rule between the ninth and the fifteenth day after operation. Post-operative bronchitis with continual coughing is an evident contributory cause of a prolapse, and so also is the lack of healing capacity, which would be expected in advanced cancer cases: this is shown by the fact that in 3 cases marked ascites was found at operation and 1 patient had both free fluid and advanced intestinal obstruction.

In 2 cases the patients were much younger, a female of 32, and a male of 46. In these cases the prolapse occurred through a left rectus colostomy incision on the first and second days respectively after operation, and were due presumably to inadequate closure of the abdominal wall round the emerging colon.

In all cases the prolapsed bowel was carefully cleaned and replaced into the abdominal cavity under gas and oxygen, spinal, or local anæsthesia, and the abdominal wall was re-sutured round the colostomy. The 9 subsequent deaths took place within five days from shock or sepsis (6 in number), or much later between the eighth and twenty-second day (3 in number), being then considered to be due to asthenia or bronchopneumonia.

Uræmia.—Urinary failure is considered to have been the cause of 6 deaths in this series. In 1 case multiple abscesses were found post mortem in both kidneys, due to obstruction of the ureters by growth; 1 man had retention of urine due to urethral strictures of long standing; 1 man died in uræmic coma; and the remaining 3 had clinical or post-mortem signs of pyelonephritis.

Malignant Cachexia.—In 5 cases patients with large inoperable carcinomata went gradually downhill after colostomy, and died at an average of twenty-one days after operation.

Miscellaneous Complications.—In this group there are 3 deaths the cause of which cannot be ascertained with accuracy, 1 death from diabetic coma, and 1 death from continued hæmorrhage from the proximal colostomy opening: this occurred in a man of 70 with an inoperable growth and secondary deposits in the liver. The bleeding from the bowel began on the thirteenth post-operative day and continued till his death three days later: it may have arisen in a malignant ulceration, or a polyp higher up the colon, or possibly from a duodenal ulcer.

DURATION OF LIFE AFTER COLOSTOMY

An inquiry into the after-histories of patients treated by palliative colostomy has shown certain facts which are set out in *Table III*. The subsequent duration of life is shown exactly in months and years according to the stage of the disease at the time of operation, a method which will, we think, be more useful than striking an average for the entire series. The following points are noteworthy:—

Operable Cases.—The 10 operable cases treated by colostomy alone were chiefly ones who refused to submit to perineal excision of the rectum after colostomy had been established. As would be expected, these patients lived for fairly long periods, half the number living for more than 3 years after operation. One patient (a man aged 66 at operation) lived for 6 years and 11 months; and one (a man aged 69 at operation) is still alive $5\frac{1}{4}$ years afterwards; in this case a very large fixed neoplasm is now present in the rectum, which a biopsy has proved to be an adenocarcinoma.*

Table III.—Duration of Life after Recovery from Palliative Colostomy (310 Cases)

	Died in Less than 3 Months after Operation	Died between 3 and 6 Months after Operation	Died between 6 and 12 Months after Operation	Survived 1–2 Years	Survived 2–3 Years	Survived 3–4 Years	Survived 4–5 Years	Survived more than 5 Years
Operable cases treated by colostomy alone	–	1 (cardiac failure)	–	2	2	2	1 (living)	2
Inoperable cases	30	33	65	71 (including 13 living)	24 (including 2 living)	11 (including 1 living)	3	1
Inoperable cases with secondary deposits in liver or peritoneum	15	21	17	4	4	–	1	–

Note.—Cases now living at a period of less than 12 months after operation are excluded from this table.

Inoperable Cases.—In this group, totalling 238, the growths were inoperable as a result of local extent and fixation to surrounding structures. *Table III* shows that rather more than 50 per cent died within twelve months after operation. A large group, 30 per cent, survived for between 1 and 2 years; 10 per cent reached the 2- to 3-year period; and 15 cases (6 per cent) survived for 3 years and more. Only one case lived for more than 5 years; this was a man aged 53 for whom a colostomy was done at a stage when he had a circular constricting growth in the rectum adherent to the base of the bladder. Four and a half years later he was re-examined; in spite of some pelvic pain he was able to do half-time work at a railway station, and his colostomy was acting well. He died 5 years and 8 months after the original operation.

* This patient has recently died, exactly 6 years after the colostomy operation.

Cases surviving for as long as this are rare, but there is a certain type of inoperable rectal carcinoma which shows little tendency to lymphatic or venous spread. After a colostomy has been established the growth remains localized in the pelvis and slowly extends until a very large fixed mass results. Pressure symptoms are often late in becoming manifest and the patient is enabled to work and be a useful member of society until an advanced stage of the disease is reached. In cases such as this a colostomy is indeed a very valuable measure for palliation.

Inoperable Cases with Metastases in the Liver or Peritoneum.—The short expectation of life in these advanced cases is indicated by the 62 cases shown in the table. More than 50 per cent died within 6 months, and 85 per cent were dead in less than a year after operation. Five cases, however, are known to have lived for *more than two years after colostomy.*

Case 10.—Male, aged 36, with a large inoperable rectal carcinoma; peritoneal secondaries found at operation; colostomy. Lived for 2 years and 1 month.

Case 11.—Male, aged 30; inoperable rectal carcinoma filling the pelvis. Secondary deposits found in the great omentum, which on section were proved to be colloid carcinoma. Lived for 2 years and 4 months after colostomy.

Case 12.—Male, aged 64; inoperable growth in rectum with a secondary nodule felt in liver at operation. Lived for about 2½ years after colostomy. Cuprase injections given after operation.

Case 13.—Female, aged 60; small mobile rectal growth proved by section to be a carcinoma. At operation the liver was found to be studded with numerous nodules which were considered to be secondary deposits, probably the result of portal vein embolism. This patient lived for 2½ years after colostomy; cuprase injections were also given after operation.

Case 14.—Male, aged 62, with an inoperable rectal growth. At operation enlarged glands were found extending high up at the root of the pelvic mesocolon, and secondary deposits were present on the peritoneum. Lived for 4 years and 2 months after colostomy.

Results such as these indicate the difficulty of making a prognosis in advanced rectal cancer. In 4 of these cases where the rectal growth was very extensive, we think the unexpected prolongation of life must have been brought about principally by the colostomy with relief of intestinal obstruction and toxæmia, and the ability to take a full diet afterwards must have aided the patients' resistance to the cancer.

Age and Sex.—We have inquired particularly into the results of colostomy when done for patients aged 70 or over, to see if there is sufficient justification for operation at this advanced age. In 66 patients over 70 years of age there were 13 operative deaths (*see Table I*). Many of the early cases in the series are untraced, but the after-histories of 41 (34 males, 7 females) are known. Seven patients (6 males, 1 female) are known to have lived for 2 years or more, the maximum length of life being 3½ years (2 male cases). The majority lived for shorter periods, and we find that the average post-operative duration of life in the 41 survivals from operation is 13 months. These facts show that colostomy can be a satisfactory operation in advanced age, particularly in males, for the operation mortality in females at this age is high, and we think that old men are, on the whole, the better subjects for the operation, both mentally and physically.

A comparison of the sexes may also be made as regards the likelihood of survival for three years or more. *Table III* shows 21 patients in this group, of whom 18 were males, and 3 females; after making due allowance for the 3 : 1 proportion of males to females in this series, this finding suggests that cancer of the rectum runs a more chronic course in males than females.

LATE COMPLICATIONS AFTER COLOSTOMY

These complications have been studied both in respect of the preceding cases of palliative colostomy, and also in a series of 370 cases of recovery after perineal excision with permanent colostomies. With regard to the function of the colostomies, we find that in 86 per cent the function has been satisfactory: certain cases have been followed up over a long course of years, and there is no doubt that with a regular routine and careful management colostomies can give good service with very little disability. Certain of the complications which will now be described have occurred to a minor degree in some of these cases, but have not disturbed the satisfactory function of the colostomies. The following complications are known to have occurred: (1) Stenosis; (2) Ventral hernia; (3) Spur retraction; (4) Prolapse; (5) Fistula into the colon.

Stenosis.—This is the most frequent complication and is due to the development of a contraction ring of fibrous tissue at the junction of the skin and mucous membrane at the colostomy: the abdominal wall musculature plays no part in it. Skin stenosis usually occurs quite early, and in some cases we have known this to happen within six weeks after the colostomy operation; moreover, it may be a very troublesome condition, which in some cases has shown a persistent tendency to recur, possibly owing to a tendency to epithelial overgrowth.

A common sequel to skin stenosis of a colostomy is a subcutaneous bulging of the colon. In these cases the colon appears to expand for a considerable extent into the subcutaneous tissues superficial to the external oblique or rectus, and the condition is due to the action of intracolonic pressure when the colostomy opening is stenosing. This bulging is most marked in obese subjects and is rarely seen in thin patients, in whom there is little subcutaneous tissue.

Treatment in early cases consists in daily, later weekly, dilatation with the finger; if this is done sufficiently early, while the scar is still soft, the contraction may be overcome. In late cases, and those in which digital dilatation has failed, a secondary operation must be done with a view to excision of the scar and an ellipse of skin round the colostomy. In addition, the actual orifice of the colostomy usually presents as a fibrous ring of inadequate size, which needs to be enlarged by incision. When a subcutaneous bulge is also present some of the overlying skin must be cut away, followed by re-suture of the mucous membrane to the new skin edge.

We have notes of 41 cases of skin stenosis, of which slightly more than 50 per cent needed operative treatment.

Ventral Hernia (*Fig.* 367).—This has occurred in a small number of cases, not exceeding 10 per cent of the total, with a slightly greater incidence in left iliac colostomies compared with those brought out through the left rectus. The largest herniæ which we have seen have been in cases in which: (1) Owing to misjudgement of the incision the colostomy has been made at the outer border of

the rectus, i.e., neither a true rectus nor a true iliac colostomy; and (2) Those in which a cup variety of belt has been worn by the patient (*Fig.* 368). In every case the bringing out of a colostomy must have some tendency to weaken the

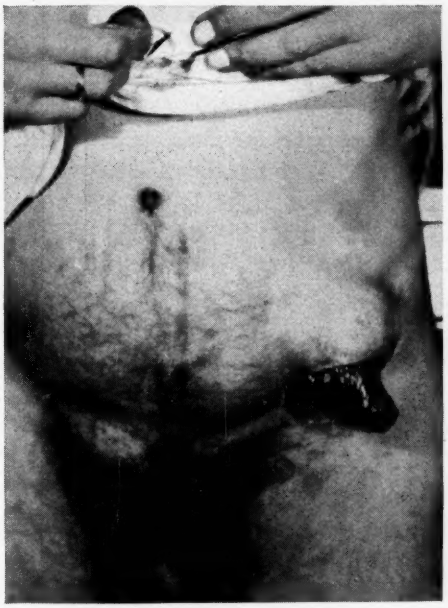

FIG. 367.—Ventral hernia.

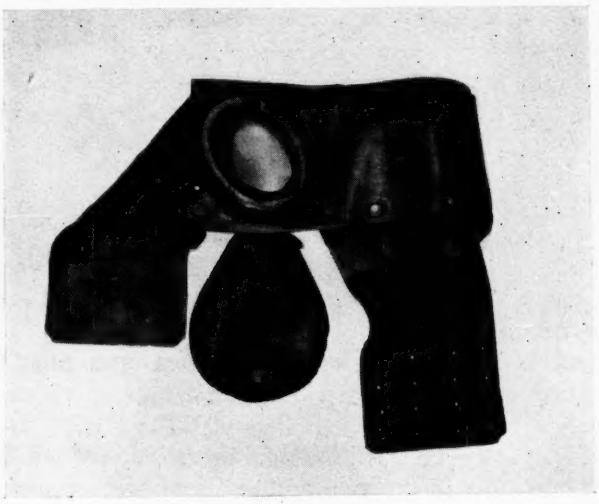

FIG. 368.—Cup belt and bag.

abdominal wall, and for this reason it should be one's aim to obtain sound primary healing of the wound, and to maintain firm support during the months immediately following operation. The wearing of the large celluloid cups which are still all too often supplied to patients by surgical instrument makers is almost certainly

followed by the formation of a large ventral hernia, which in time seriously interferes with the colostomy function.

This complication is one which it is eminently better to prevent rather than to cure, and this can be done chiefly by careful operative technique, by aiming at subsequent asepsis, and the wearing of a flat supporting belt. Only in rare cases is it necessary to perform a reparative operation.

Spur Retraction.—This is an important complication which results in complete dysfunction of the colostomy, with passage of fæces into the distal colon, and is often found in conjunction with stenosis, subcutaneous bulging, and ventral hernia. Retraction occurs most commonly in cases in which owing to shortness of the mesocolon, or to excessive depth of fat in the abdominal wall, it has proved difficult to bring the colon to the surface. Undue tension subsequently takes place in the bowel, and there may be a persistent tendency to retraction. Various devices may need adoption to deal with the difficulty and prevent the occurrence of this complication: (1) At operation thorough mobilization of the colon by incision of adventitious peritoneal folds usually found on the outer side of the mesocolon; (2) Excision of wedges of subcutaneous fat round the incision; or, rarely (3) Abandoning the plan of making an iliac or pelvic colostomy in favour of a transverse colostomy through a new incision. If a 'rod' colostomy is made, the rod should be left *in situ* for at least fourteen days in order to get the colon well adherent above the abdominal wall; alternatively, a 'bridge' colostomy may be done by bringing a strip of skin or aponeurosis (rectus sheath or external oblique) through a hole in the mesocolon. It should be noted, however, that if a skin bridge is used, there appears to be some additional risk of late skin stenosis, to avoid which excision of skin round the colostomy is necessary.

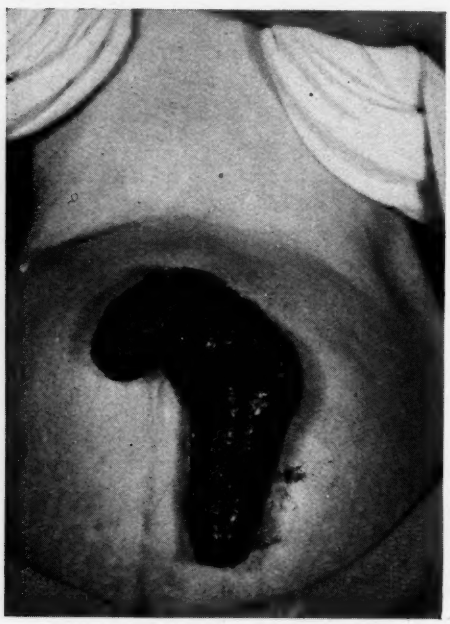

FIG. 369.—Prolapse.

The treatment of a colostomy with a retracted spur must be operative and consists in dissecting out the retracted bowel and refixing by one of the methods mentioned above.

Prolapse (*Fig.* 369).—This is a rare complication, and we have notes of only 12 cases in this series. As in the case of rectal prolapse, a colostomy prolapse may be complete (entire thickness of colon) or incomplete (mucous membrane only); it usually takes place from the upper opening, or occasionally from the lower or both, openings. Prolapse is always associated with a patulous opening in the abdominal wall. Treatment in slight cases is by firm support, and in severe cases when the patient is much troubled by mucoid discharge, amputation of the prolapse becomes necessary and can be effected with only slight risk.

Fistula into the Colon.—This we have known to occur in 2 cases; it has probably been due to ligation of appendices epiploicæ which have happened to contain diverticula. This complication can be prevented by leaving untouched any thick appendices which are found arising from the colon near the skin level; instead of excising them for neatness it is preferable to leave them or tuck them back beneath the skin level.

TECHNIQUE OF COLOSTOMY

Preparation.—Unless the patient is definitely obstructed, a palliative colostomy is not to be regarded as an emergency operation. A slight degree of abdominal distension will in most cases subside if the patient is put to bed on a fluid diet, with small repeated doses of liquid paraffin and saline aperients: glycerin enemata should be given if necessary. The mouth should be cleaned up, the urea excretion should be estimated, and steps taken to improve it if possible. The condition of the heart and lungs must be estimated, and thought given to the most suitable type of anæsthesia. With rest and careful preparation on these lines we believe that much can be done to lower the operative mortality in these cases.

Incision and Fixation of the Colon.—The tendency at St. Mark's Hospital in recent years has been to perform an increasing proportion of colostomies through a left oblique muscle-splitting incision. The advantages of this incision are:—

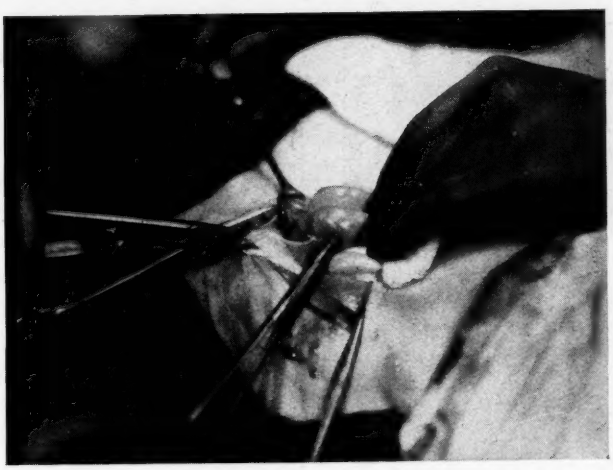

FIG. 370.—Closure of the lateral space.

1. It is placed directly over the iliac colon, which can usually be brought comfortably to the surface, leaving the pelvic colon undisturbed should any further operative procedure be planned from below.

2. The lateral space between the emerging colon and the parietal abdominal wall can be readily closed by suture, thus preventing the possibility of small-intestinal strangulation here.

3. The figures already adduced show that prolapse of the small intestine is rare through an oblique incision when compared with a rectus or paramedian incision.

Against this it must be admitted that a left rectus incision has some advantages in that the colostomy is placed in a slightly better position for the patient's management, and there may be less likelihood of a subsequent incisional hernia; but after assessing these various points we believe that a left oblique colostomy, if done with attention to the following points, is the safest and most satisfactory method, particularly when done in conjunction with a careful abdominal exploration through a right paramedian subumbilical incision.

A 'gridiron' incision, 4 in. long, is made in the left iliac region; occasionally it may be necessary to incise the internal oblique for an inch transversely to its fibres at the medial end of the incision. The iliac colon is found immediately deep to this incision and is brought out, being held gently in a wet pack. On doing this a peritoneal fold is produced running outwards and forwards from the lateral aspect of the bowel to the cut edge of the parietal peritoneum. A No. 0 catgut suture on a curved atraumatic needle is passed from within outwards along the free edge of this fold, and when tied effectively closes what would otherwise become an artificial foramen (*Fig.* 370). A glass rod $\frac{3}{4}$ in. in diameter, and $3\frac{1}{2}$ to 4 in. in length, with smooth rounded ends, is now passed through the mesocolon immediately above the stitch along the lateral fold. Injury to the veins can usually be avoided by selecting an avascular part and gently pressing into it one end of the rod, while an assistant with a pair of non-toothed dissecting forceps scratches on to the rod as it is made to present on the opposite side. The rod is prevented from slipping out by placing on each end a separate piece of rubber tubing. (A half circle of tubing is cumbersome and does not seem to have any additional advantage.)

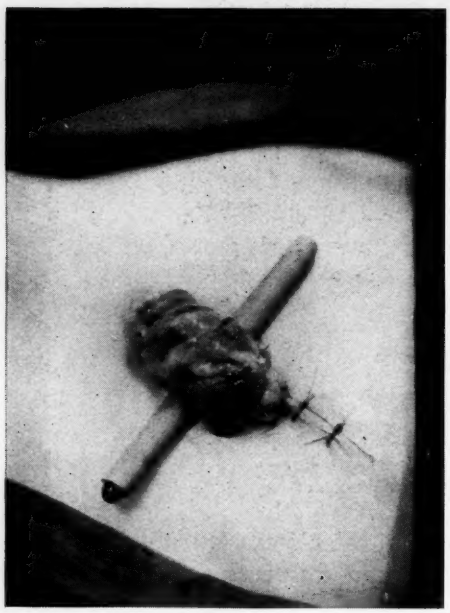

FIG. 371.—Finished colostomy.

Closure of the Wound.—The peritoneum is closed above and below the bowel with No. 1 chromic catgut, leaving a space which will take both limbs of the colostomy without undue compression. In practice it is found advisable not to close the peritoneum so tightly that a finger cannot fairly be passed in alongside the bowel. The internal oblique is sutured if necessary, and the external oblique is repaired with interrupted catgut sutures, each of which takes up a small portion of the underlying muscle. We attach some importance to this point, for it ensures closure of an intermuscular space into which the colon might subsequently bulge. Care must be taken not to suture the external oblique too closely to the bowel, and in addition it is often advisable to make short relieving incisions, with blunt-pointed scissors, into the sharp edges of the external oblique aponeurosis. These incisions are made at right angles to the fibres opposite the centre of the space left for the emerging bowel. An ellipse of skin is excised from both margins of the wound immediately opposite the colostomy

to avoid the common late complication of skin stenosis. The remainder of the wound is closed with interrupted silkworm-gut sutures, which include the external oblique and thus obliterate a potential subcutaneous space into which the bowel at a later date has not infrequently become herniated. (*Fig.* 371.)

Ligation of Appendices Epiploicæ. — Redundant appendices epiploicæ are now ligated and excised; this should be done principally in relation to the prominent part of the colon, with care not to ligate any appendices which arise close to the skin level.

FIG. 372.—Elastoplast dressing.

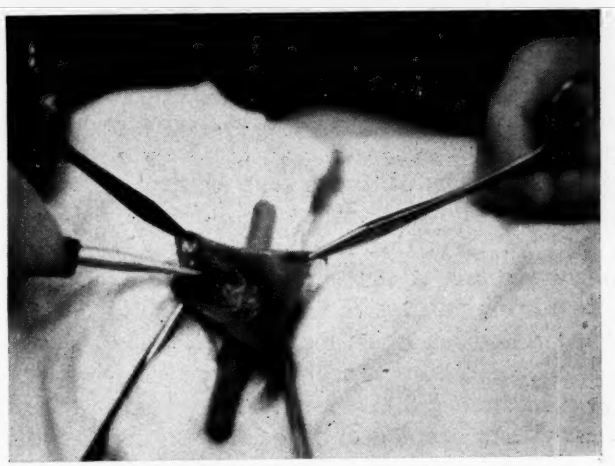

FIG. 373.—Opening the colostomy with a cautery.

Dressings and Immediate Opening of the Colostomy.—If a paramedian exploratory incision has been made, it is dressed with gauze and sealed with elastoplast. The colostomy incision is dressed similarly, and after carefully tucking flat pieces of dressing gauze under the rod, a supporting transverse strip of elastoplast

is placed each side (*Fig.* 372). The wound is additionally protected by sterile towels and packs, and with a Paquelin or Post cautery the colostomy is now opened widely by transverse and longitudinal incisions (*Fig.* 373). Any solid fæcal masses which present are removed. The immediate introduction of about 5 oz. of warmed olive oil into the proximal limb of the colostomy has, we think, proved beneficial to patients (*Fig.* 374). The oil can be run in easily through a No. 16

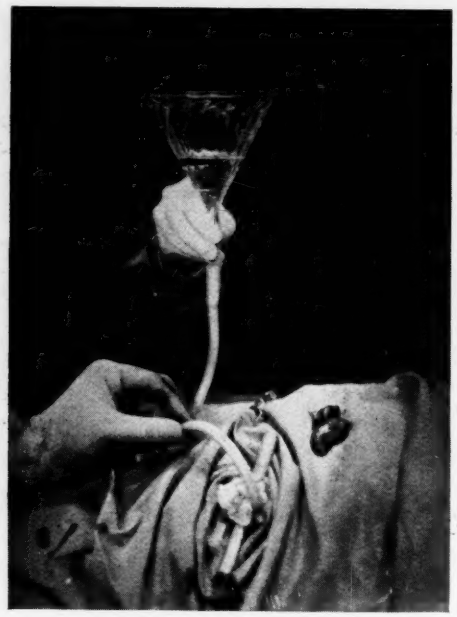

FIG. 374.—Introduction of olive oil.

rubber catheter; it is always retained and greatly assists in lubricating the bowel and allowing the easy passage of flatus. Finally a dressing of dry gauze and wool is applied.

Subsequent Care.—The patient is kept for the next week on a low-residue, chiefly fluid diet. As a rule colostomy wash-outs are inadvisable before removal of the sutures, and we think that most patients run a quieter and more comfortable post-operative course if wash-outs into the proximal bowel are not given. Small doses of liquid paraffin may be given on the third day after operation, and usually a colostomy action begins on the fourth day.

Flatus is passed per colostomy from the time of operation, and the absence of post-operative pain from gas distension of the colon is very marked in those cases in which immediate opening of the colostomy has been done. The Ward Sisters in charge of large numbers of colostomy cases are in a good position to give an opinion on this matter, and we find among them a general agreement as to the almost complete absence of post-operative pain after laparotomy and colostomy with immediate opening of the bowel. The elastoplast is removed on the third or fourth day and the underlying gauze changed: primary healing has been obtained in practically all cases treated by this method. Sutures are removed from the colostomy incision about the sixth or seventh day. The glass rod is left *in situ*

for fourteen days and may then, with advantage, be replaced by a rubber tube with over-turned ends to prevent it slipping out (*Fig.* 375); this tube can be left for another one or two weeks before final removal, and helps to maintain a good spur until the bowel is firmly adherent.

With regard to the subsequent management of the colostomy there are these two alternatives: (1) The training of the bowel by careful dieting and regular meals until the habit of regular colostomy actions once or twice a day has been established; and (2) The giving of a soap and water wash-out into the proximal colon at a regular time each day, morning or evening. This routine has some

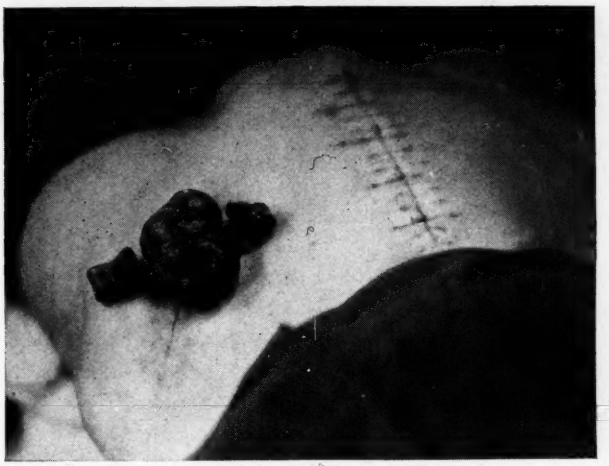

FIG. 375.—Rubber tube substituted for glass rod.

advantages, especially for manual workers, and in many of these cases has been satisfactory over a long period of years. There are, however, some patients who after continued wash-outs develop a chronic catarrh of the colon, with excessive formation of mucus and sometimes irregular or incomplete return of the daily wash-out. At the same time there is a loss of the natural dilating effect of formed fæces upon the colostomy opening. For these reasons we think that after colostomy a patient should be encouraged first to try and obtain natural colostomy actions; if this fails for reason of loose or irregular actions, then the daily wash-outs must be started.

In very infirm subjects and in those lacking responsible relatives or nursing facilities at home, the arrangements for the patient's subsequent after-care need to be carefully considered, and in the poorer classes permanent institutional treatment is often desirable after colostomy.

SUMMARY

1. The value of palliative colostomy for rectal carcinoma and the operative mortality is discussed.

2. The causes of death have been analysed and the duration of subsequent life has been shown, together with the late complications.

3. An operative technique for colostomy has been described, an important

feature being the immediate opening of the bowel. This is applicable both to obstructed and non-obstructed cases; it has already considerably reduced the mortality rate and will, we think, prevent many of the late complications.*

The statistical information regarding these cases has been obtained from the Cancer Follow-up Scheme of St. Mark's Hospital, which has been financed by the Medical Research Council since 1922. We are indebted to Mr. H. J. R. Bussey, B.Sc., of St. Mark's Hospital, for the photographs illustrating this article.

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[1] GABRIEL, W. B., *Proc. Roy. Soc. Med.*, 1928, xxi, 1433.

* In 41 operations with this technique for inoperable rectal cancer there have been 2 deaths (5 per cent). In a further 23 operable cases there have been no deaths attributable to the colostomy.

ADENOMATA OF THE PITUITARY, WITH SPECIAL REFERENCE TO PITUITARY BASOPHILISM OF CUSHING

By WILLIAM SUSMAN

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In the past, benign tumours of the anterior pituitary have been considered important because in some cases they gave rise to acromegaly, and in others to disturbances chiefly due to mechanical reasons. In recent years, however, Cushing[1] has described a clinical syndrome which he has termed 'pituitary basophilism', and which he considers to be due to hypersecretion arising from a basophilic adenoma or basophilic hyperplastic area in the anterior pituitary. Cases showing this syndrome have a rapidly acquired and painful adiposity, lumbospinal pains, sexual dystrophy, hypertrichosis, and a dusky skin.

If the syndrome described by Cushing is due to the hypersecretion of the basophilic cells in an adenoma or in a hyperplastic area in the anterior pituitary, then such lesions must be closely associated with cases showing this syndrome. However, if tumours of this type are common, then they are of no etiological significance, and their presence in these cases is only due to chance.

In the endocrine glands the whole question of benign tumours is intimately bound up with the process of hyperplasia in its general sense; in other words, many, if not the majority, of such growths are in all probability not neoplasms in the true sense. If these benign tumours are hyperplastic rather than neoplastic, then, as tissue damage and repair are usually associated with hyperplasia, such changes should be present in any series including a considerable number of pituitaries. An investigation of a series of 260 hypophyses obtained from routine post-mortem examinations showed that the hypophysis in this respect did not differ from the remainder of the ductless glands. In short, as the hypophysis is damaged quite frequently, repair in that organ is not uncommon, and therefore it is not in the least surprising that so-called adenomata or hyperplastic areas should occur.

The series forming the basis of this investigation is made up of 260 cases examined at the Manchester Royal Infirmary in the course of the routine necropsy examinations. The gland was examined in all cases in which the cranial vault was opened. The only limiting factors were time and the condition of the tissues. The hypophysis of each case was cut antero-posteriorly through the infundibulum and fixed in Helly's fluid. Each half of the gland was prepared for paraffin sections, and those sections from the infundibulum region were stained by hæmalum and eosin. When in doubt, acid fuchsin-methyl green or Weigert's iron-hæmatoxylin and eosin methods were utilized. Both of these latter methods differentiate the cells of the anterior pituitary very well. On the whole, it must be considered that the infundibulum region alone was examined, although a few of the glands were examined in serial sections.

Of the 260 glands in this series, 22 contained 23 tumours, and, of these, 20 were of a purely incidental character and had given rise to no symptoms. The

histories from these tumour cases were quite typical of the disease evident at the time the patient was admitted into hospital, and at the time of death. The cases in which the tumours had given rise to symptoms were: (1) A case of acromegaly in which the anterior pituitary contained an acidophilic adenoma (6 × 8·5 mm.); and (2) A case in which an acidophilic adenoma 25 mm. in diameter had given rise to pressure symptoms. Thus benign tumours of an incidental character occurred in about 8 per cent of the cases of this series.

The incidental tumours varied from 0·2 mm. in diameter to 7 × 3·5 mm. Of the acidophilic type there were 4 (1·6 per cent), of the basophilic 8 (3 per cent), and of the chromophobe 5 (2 per cent). The remainder formed a miscellaneous group; in one case the tumour was made up of columnar cells, while in 3 others small tumours consisting of greyish cells of a rather indifferent appearance were present in the infundibulum and in the pars nervosa. The full details are shown in *Table I.*

Table I.—PITUITARY ADENOMATA, 23 CASES (2 IN 1 CASE)

		Size in mm.
Basophilic.—		
M. 49.	Pernicious anæmia	1·5
F. 26.	Acute encephalitis	1 × 0·5
F. 57.	Otitis media	0·3
F. 40.	Pellagra and confusion (*Fig.* 376)	0·3
M. 52.	Acute mastoiditis (*Fig.* 377)	1·5 × 2·3
F. 22.	Diabetes mellitus	1·5
M. 36.	Addison's disease (tuberculosis)	0·2
M. 31.	Glioma	5 × 2
Acidophilic.—		
M. 58.	Shock following fall	0·3
F. 24.	Pituitary adenoma	25·0
M. 17.	Renal infantilism	2·0
M. 26.	Fracture skull, meningioma dura	0·2
F. 62.	Pellagra and acute pancreatitis	7 × 3·5
F. 66.	Acromegaly	6 × 8·5
Chromophobe.—		
M. 25.	Glioma and miliary tuberculosis	1·0
M. 42.	Cerebral hæmorrhage	1·5
F. 44.	Addison's disease	1·8
M. 42.	Tabes	0·4
M. 55.	Cerebral hæmorrhage	0·2
Miscellaneous.—		
F. 55.	Cerebral hæmorrhage, columnar-celled	0·6
M. 48.	Cerebral hæmorrhage (in infundibulum)	0·3
F. 37.	Diabetes mellitus (pars nervosa)	1·5
M. 50.	Ruptured cerebral aneurysm (in infundibulum)	0·3

In *Table II* the age and sex incidence of this group of tumour cases is compared with those of the whole pituitary series.

The available data show, therefore, that incidental tumours occurred in 8 per cent of the cases in this series when the gland was examined in the infundibular region only. Had the glands been further examined, then most probably the incidence would have been proportionately higher. Further, the basophilic tumour was the commoner type present. The age and sex distribution were roughly comparable with those of the general series. Nor did the diseases prevalent in these

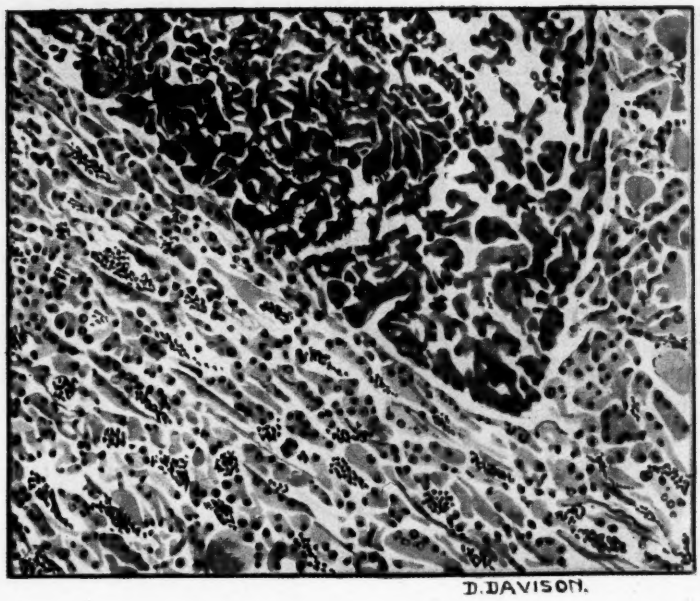

FIG. 376.—*Case* 1. Female, aged 40. Pellagra. The tumour is about 0·4 × 0·6 mm. and consists of basophilic cells which are about normal in size. The growth is well demarcated from the glandular tissues. (Stained by hæmalum and eosin.)

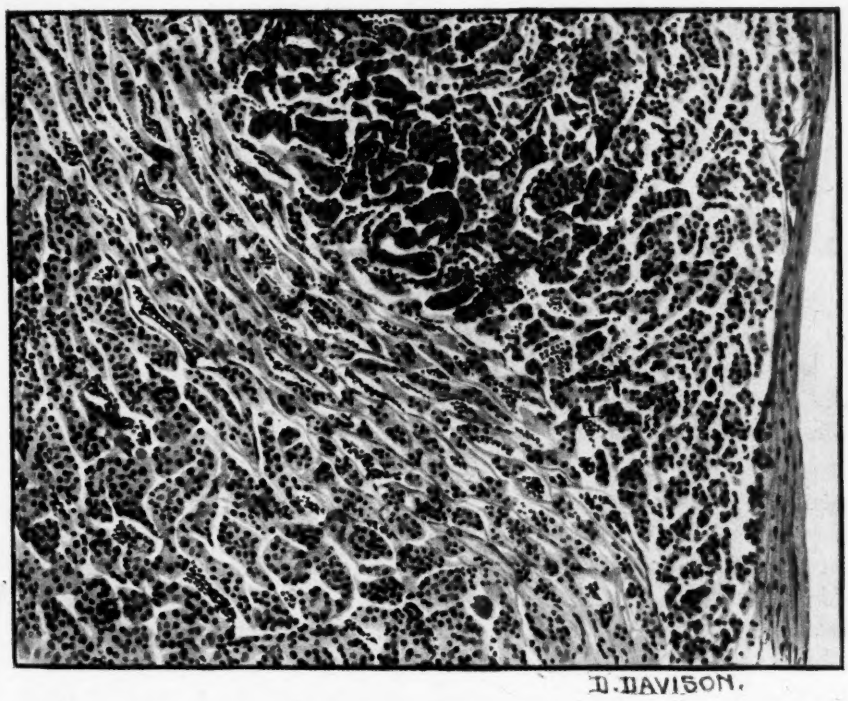

FIG. 377.—*Case* 2. Male, aged 52. Acute mastoiditis. The tumour is 1·5 × 2·3 mm. and is made up of basophilic cells of the small hyperplastic type. The nodule is quite distinct from the surrounding glandular tissue. (Stained by hæmalum and eosin.)

cases give any specific indication, but, on the contrary, they varied greatly. Pellagra was present in 2 cases, cerebral hæmorrhage in 4, and tumours in 4, while the remaining cases were each of a different type. All had histories typical of the disease indicated for each case. These tumours therefore occurred in no specific age, sex, or disease group. This applied equally well for each of the several types of incidental adenomata of the anterior pituitary.

Table II.—Age and Sex Incidence of Pituitary Tumours

Age Group	Adenoma Series				General Pituitary Series		
	M.	F.	Total	Per Cent	Number	Per Cent	Per Cent of Adenoma Cases in each Age Group
0–9	–	–	–	–	16	7·6	0
10–19	1	0	1	4	25	10·0	4
20–29	2	3	5	23	38	15·2	13
30–39	2	1	3	14	34	13·6	9
40–49	4	2	6	27	52	20·8	12
50–59	5	0	5	23	47	16·8	11
60–69	0	2	2	9	25	10·0	8
70 +	–	–	–	–	9	3·6	0
Totals ..	14	8	22	100	246*	–	–

* Males 151, females 95.

Then in what way do these tumours differ from the actively secreting tumours of the acromegalic? The size of the tumour is no certain indication, as can be seen from *Table I.* In the acromegalic tumour the cells are hypertrophied (*Fig.* 378). In contrast, the cells of the incidental tumours (*Figs.* 379, 380) and of the tumour which gave rise to pressure symptoms (*Fig.* 381) were hyperplastic, and from a functional standpoint these cells were probably ineffective. This one may reasonably infer from what occurs in the thyroid.

Table III.—Basophilic Cells High in 21 Cases *

Age Group	No. of Cases
0–9 ..	2
10–19 ..	1
20–29 ..	3
30–39 ..	0
40–49 ..	6
50–59 ..	6
60–69 ..	1
70 + ..	1

* Males, 16; females, 5. Age in 1 case not available.

But even if the basophilic adenomata had produced an effective and distinctive secretion, what type of symptoms might one expect? The whole series of 260 cases included 21 cases in which the basophilic cell content of the anterior pituitary was definitely high. A study of these cases showed that the age and sex incidences were those of a fair sample (*Table III*). Acute diseases accounted for 5 cases, tumours for 5, chronic nephritis for 2, and epilepsy for 2. The remaining cases were each of a different type. Thus, an abundance of basophilic cells in the

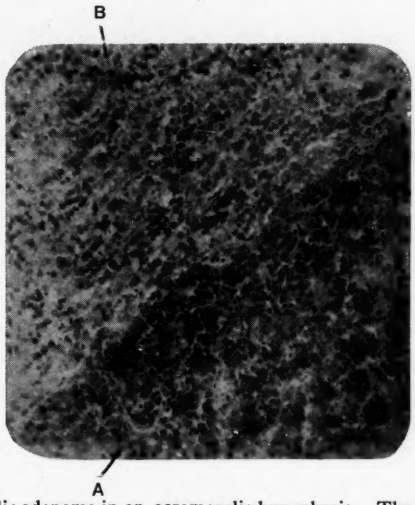

FIG. 378.—A, The acidophilic adenoma in an acromegalic hypophysis. The cells are larger than those in the other types shown in *Figs.* 379–331. B, The neighbouring anterior pituitary tissue. (×130.)

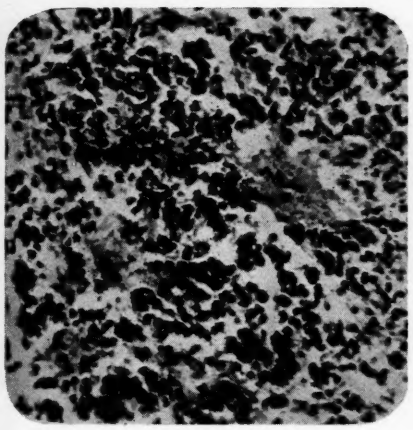

FIG. 379.—Small hyperplastic cells in an incidental acidophilic adenoma. (× 130.)

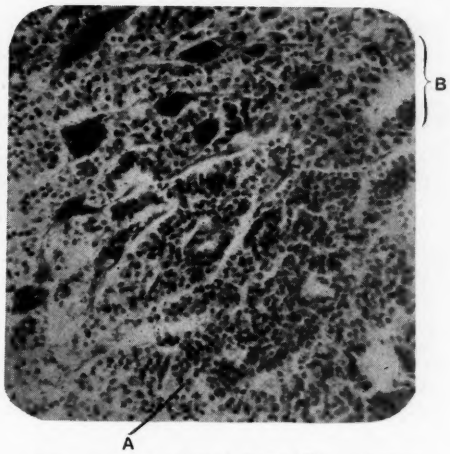

FIG. 380.—Incidental basophilic adenoma which is made up of small hyperplastic cells. A, Tumour; B, Anterior pituitary. (× 130.)

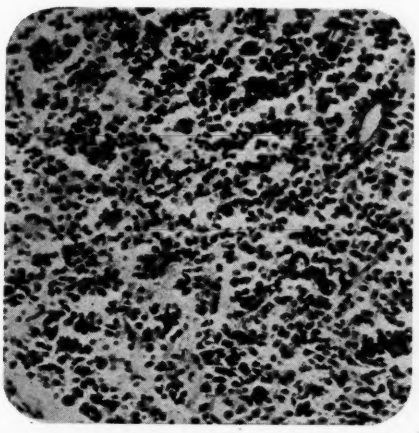

FIG. 381.—An acidophilic adenoma made up of small hyperplastic cells; it had given rise to pressure symptoms. (× 130.)

anterior pituitary is not peculiar to any age, sex, or disease group. If these cells produced a hormone important to the sex mechanism of the individual, a definite difference could be expected, both with justification and without exception, as between infants and children as sexually immature and practically sexless on the one hand, and the adults on the other. This, however, was not the case, as the figures in the tables have indicated. The incidence of cases showing a high basophilic cell content in the anterior pituitary was high between the ages of 40 and 60 years, but almost 40 per cent of all the cases in the whole series belonged to this age period.

The conclusion is, therefore, that the histological data from this series of 260 hypophyses give no support to the contentions either of Zondek,[2] that the basophilic cells of the anterior pituitary secrete a sex hormone, or of Cushing, that hypersecretion of basophilic cells caused by the presence in the anterior pituitary of a basophilic adenoma or of an area of basophilic hyperplasia will give rise to the syndrome which he has termed 'pituitary basophilism'. Adenomata as a whole occur in 8 per cent of cases, the basophilic type in 3 per cent, and they are therefore too common to be of any special significance.

I wish to thank Dr. Tattersall, of the County Mental Hospital, Prestwich, for the acromegalic hypophysis, and Mr. H. C. Taylor for his care in preparing the photomicrographs.

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[2] ZONDEK, B., *Klin. Woch.*, 1933, xii, 1.

PERFORATION OF CARCINOMA OF THE STOMACH INTO THE GENERAL PERITONEAL CAVITY

By IAN AIRD

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A HUNDRED and ten years ago Laennec noted in his case book, " Ventriculus hodie ruptus est in loco scirrhi et jam peritonitis adest et tympanites peritonealis ",[40] and few since have been fortunate enough to make such a diagnosis with the same confidence and the same accuracy. Still to-day no clear clinical picture assures for us the pre-operative recognition of perforated carcinoma of the stomach; the infrequency of this catastrophe in even the widest surgical practice and the lack of a comprehensive English description of the condition conspire to render exact diagnosis uncertain. A study of the details of available cases is thus justified, and the rarity of a correct diagnosis—definitely claimed in only five reported cases—renders such a study not only justified but imperative. In the consideration of perforated carcinoma of the stomach which follows, one case of the writer's will be described, 7 other cases treated in the Royal Infirmary, Edinburgh, during the last ten years will be summarized, and with these will be examined 71 cases collected from the available literature.

CASE REPORTS

Case 1 (author's case).—A ship's mate, aged 27, was seized while out walking by epigastric pain, slight at first, but increasing gradually to become intense after an hour, and generalized then over the whole abdomen. Vomiting of yellow fluid was frequent thereafter, but failed to relieve the pain. Slight irregular epigastric pain, not consistently related to food, had been present untreated for some years. This pain had been more severe, and almost continuous for a few weeks before admission to hospital. No vomiting or melæna had occurred, and there had been no loss in weight.

ON ADMISSION.—On admission to hospital, six hours after the onset of the attack, the pain eased and the vomiting ceased. The temperature was 97·6°, pulse 120, regular, and soft; respirations 22. Tenderness and rigidity were intense and generalized, but maximal in the epigastrium. No distension was present, a palpable tumour was not felt, and there was no dullness in the flanks. Liver dullness was diminished.

OPERATION.—A diagnosis of perforated peptic ulcer having been made, the abdomen was opened by a right paramedian rectus-displacing incision, under gas and oxygen anæsthesia. The peritoneal cavity was evacuated of gas and of about one pint of serofibrinous straw-coloured exudate. The parietal and visceral peritoneum was everywhere congested. No perforation was found on the anterior wall of the stomach or duodenum, but the omental bursa having been opened through the transverse mesocolon, a perforation was found on the posterior wall of the stomach, 1 in. in diameter, and situated near the lesser curvature about 2 in. from the pylorus. The edges of the opening were ragged, white, and crumbling, and the perforation had occurred through the posterior flap of a saddle-shaped ulcer which involved the lesser curvature and the greater part of the girth of the stomach. No suspicion arose that this ulcer might be malignant, until a mass of large hard glands was observed in the lesser omentum. One of these was excised. An attempt was now made to close the perforation—a matter of extreme difficulty on account of the friability of the diseased stomach wall around the opening.

Gastrectomy seemed at one point the only solution, but ultimately a closure was effected by mattress sutures, and the closed perforation was overlaid by transverse mesocolon. A suprapubic stab incision was made for the transmission of a drain to the rectovesical pouch, and the paramedian wound was closed in layers. Section of the excised omental gland proved it to be replaced by a highly cellular adenocarcinoma with no glandular arrangement whatever. Immediate recovery was uneventful, but the degree of glandular metastasis was so great that a radical operation was not performed, and the patient returned home.

During convalescence a test-meal was given and the free acid estimated at 3·5, the total acidity at 11·5 Ewald units. No organic acids were present. X-ray examination before discharge from hospital showed a six-hour residue of barium in the stomach, a large crater on the posterior wall, and some reflux of barium into the œsophagus.

Case 2.—A gardener, aged 70, was admitted to hospital with a history of seven hours' severe, persistent, umbilical pain of sudden onset, accompanied by the vomiting of dark brown fluid. Epigastric pain, a few hours after food, and accompanied sometimes by vomiting, had troubled the patient at intervals for forty years, but had been recently improved by medical attention. The abdomen was markedly and diffusely tender and rigid. At immediate operation gas and gastric contents were present in the general peritoneal cavity, and a perforation through a large ulcerative prepyloric tumour was found. This was closed, and the peritoneal cavity drained. Recovery was satisfactory for sixteen days, after which the patient began to go downhill, and death occurred on the twenty-third day, probably from subphrenic abscess.

Case 3.—A coal-miner, aged 45, was attacked suddenly a few hours before operation by a sharp stabbing epigastric pain with rigidity of the abdominal muscles. This sudden pain occurred while the patient was undergoing treatment in a medical ward for epigastric pain of two years' duration, increased by food, relieved by vomiting, and culminating in a recent hæmatemesis. The free acid had been estimated at 70, the total acidity at 100 in the fasting juice, 30 and 50 respectively, rising steadily for two hours, after test-meal. At operation a great deal of free fluid was found in the peritoneal cavity, and, in the stomach, a large saddle-shaped prepyloric ulcer, fixed and irremovable. The perforation was closed, an enlarged gland excised for examination from the lesser curvature, and the peritoneal cavity drained. The excised gland was shown microscopically to be replaced by masses of undifferentiated cells, with in scattered areas an attempt at gland formation. The patient made a good immediate recovery and left hospital on the eighteenth day of convalescence.

Case 4.—A man, aged 65, was admitted with a subnormal temperature, an almost imperceptible pulse, and a cold clammy skin, too ill to give a clear history, but having suffered for twelve to eighteen hours from gradually increasing abdominal pain, mainly right-sided. Vomiting occurred once or twice. Operation was performed at once, pale yellow serous fluid found in the peritoneal cavity, and a large perforation, impossible of closure, discovered in a tumour of the lesser curvature. Jejunostomy was performed, but death occurred in forty-eight hours. The post-mortem examination revealed an early fibrinous peritonitis, from a perforated irregular ulcer of the lesser curvature. The stomach wall presented a hard diffuse infiltration around the ulcer; numerous secondary deposits were present in the omental glands and in the liver.

Case 5.—A man, aged 57, was suddenly attacked by severe epigastric pain, unaccompanied by vomiting, and persisting without alleviation till admission to hospital six hours later. For fifteen years epigastric discomfort had been present, coming on half an hour after food, sometimes accompanied by vomiting of food, but relieved by sodium bicarbonate or the taking of more food. This history, supported by extreme rigidity of the upper abdominal muscles, encouraged a diagnosis of perforated gastric ulcer. At operation, which was performed immediately, gas and turbid fluid were evacuated from the peritoneal cavity. The parietal and visceral peritoneum was everywhere inflamed, and a perforation, $\frac{1}{4}$ in. in diameter, was found on the anterior wall of the stomach, midway between cardia and pylorus, through an ulcerating tumour. Enlarged glands were present in the lesser omentum, but no other metastases were found. The perforation was closed, and gastro-enterostomy performed, but death followed within twenty-four hours.

Case 6.—A man, aged 70, gave a history of severe lower abdominal pain of sudden onset and twenty-four hours' duration. The last meal taken had been vomited. After twelve hours there was some lessening of the pain, but its initial intensity was shortly renewed and surpassed. There had been one month's previous indigestion—slight epigastric pain one hour after food, unrelieved by alkalis or by the taking of more food. This had been accompanied by considerable loss in weight. Generalized abdominal rigidity was present, maximal in the epigastrium. Some tenderness was elicited in the hypogastrium and right iliac fossa, and the presence of free fluid in the peritoneal cavity was suspected. At operation yellowish fluid, suspending flakes of fibrin, was found in the peritoneal cavity. The whole stomach was generally infiltrated by malignant disease. The actual perforation was not with absolute certainty detected, but a leakage was suspected from a point on the lesser curvature. Enlarged glands were present both in the lesser omentum and in the gastrocolic ligament. Drainage of the peritoneal cavity was effected, but death occurred four days later. Section of an omental gland had all the appearances of a typical adenocarcinoma.

Case 7.—A deaf-mute butcher, aged 72, was attacked suddenly by severe epigastric pain, vomited foul-smelling fluid once, and was admitted to hospital a few hours later. Difficulty of communication with the patient prevented any elicitation of an indigestive history, but he admitted some recent loss in weight. General tenderness and rigidity were present, maximal just to the right of the umbilicus. Slight distension was observed, no free fluid was apparently present, and no tumour was felt. On a diagnosis of perforated peptic ulcer, immediate operation was performed; turbid fluid was evacuated, and a perforation found and closed with difficulty: this had occurred through an obviously malignant ulcer of the anterior wall of the stomach which was partly adherent to the peritoneum of the abdominal wall. An enlarged gland was excised from the lesser curvature, but showed no malignant invasion. Death occurred forty-eight hours after operation, but a post-mortem examination was refused.

Case 8.—A housewife, aged 56, gave a history of a severe attack, sudden in onset, of generalized, cramping abdominal pain, of eight hours' duration. For four years previously a heaviness had been complained of in the epigastrium, just to the left of the mid-line. No vomiting occurred. Food failed either to relieve or to increase the feeling of weight, which had no relation to meals. Recent loss of weight had been noticed. Epigastric rigidity and tenderness led to a diagnosis of perforated peptic ulcer, and immediate operation was performed. A large quantity of brown fluid found in the peritoneal cavity was evacuated, and a perforation through a carcinoma of the anterior wall of the pyloric antrum was closed with difficulty. No metastases were present. The patient made a good recovery and was discharged in three weeks, with the promise of a later gastrectomy, but on reporting later, a large mass already palpable in the epigastrium, and clinical evidence of liver metastases, forbade any further intervention.

ANALYSIS OF CASES OF PERFORATED CARCINOMA OF THE STOMACH

Chavannaz and Radoiévitch,[16] in a detailed and authoritative survey of perforated cancer of the stomach, with a collection from the literature of 46 cases, group the reported cases in four clinical categories: (1) Cases of sudden severe epigastric pain, accompanied by all the text-book signs of gastroduodenal perforation, and preceded by a history of indigestion. (2) Cases complaining of epigastric pain of similarly sudden onset, but with no previous dyspeptic phenomena; (3) Cases exhibiting the signs of a gradually progressive peritonitis; (4) Cases in which death occurs without attention being directed to the abdomen. It will be simpler, however, to merge the first two of Chavannaz's categories, which differ from each other only in the presence or absence of previous indigestion, and to combine also his third and fourth groups, since the fourth group may be considered merely as cases of gradual peritonitis insidious enough to escape the clinician's notice.

Of the 79 cases reviewed in the present paper, only 67 are reported complete with clinical histories. Of these, 44 (66 per cent) fall into the first group of fulminating cancerous perforation of the stomach into the general peritoneal cavity, and their histories correspond with those of seven of the cases reported above, and, incidentally, with the histories of typical perforated peptic ulcers. The remaining 23 (34 per cent of fully reported cases) share an absence of acute initial pain: in other respects their symptoms vary widely. These can be termed conveniently silent perforations of gastric carcinoma into the general peritoneal cavity, and among them is included the fourth case reported above. The 12 cases whose clinical histories are lacking are useless in an analysis of symptoms, but their operative and pathological findings will be referred to later.

I. FULMINATING PERFORATIONS OF CARCINOMA OF THE STOMACH INTO THE GENERAL PERITONEAL CAVITY*

This, the commoner variety of malignant perforation of the stomach, includes two-thirds of the fully reported cases. The age incidence resembles that of carcinoma of the stomach, ranging from 23 to 78; 55 per cent of the cases fall in the 40–60 age period. Males suffer more than females in the proportion of 3 to 1.

All give symptoms now recognized as typical of gastroduodenal perforation—sudden severe epigastric pain often relieved spontaneously, but temporarily, after a few hours. The presence of vomiting is commoner than its absence, and hæmatemesis occurred in one case.[60] If operation is not performed, death occurs in one quarter of the cases within twenty-four hours of the onset of the pain, and one case in seven dies within six hours. Four cases lived longer than ten days without operation, and one lived for six weeks, in spite of an acute onset, a definite perforation, and, after death, the appearances of peritonitis. Of the 20 cases which came to operation, 70 per cent gave less than a twelve-hour history of pain. It is noteworthy that in half the cases perforation occurs while the patient is in bed, either at hospital or at home, under treatment usually for indigestion. In only one case is the patient specifically stated to have been up and about at the moment of perforation.

Previous Indigestion is extremely varied, but in long-standing cases a recent increase in severity is often observed. In only three cases is previous dyspepsia denied; in one-third of the cases it has been present for more than two years, and in one-sixth for more than five years. Previous hæmatemesis is more commonly admitted than denied.

Physical Examination elicits rigidity and tenderness suggestive of perforated peptic ulcer in four-fifths of the fulminant cases. A tumour mass is rarely palpated. The test-meal was examined in 8 cases, and in only 2 of these was achlorhydria present. In one case the acidity is described as normal, and in another free acid is stated to have been present, and total acidity to have measured 55 Ewald units. The remaining four cases gave figures of 3·5 and 11·5, 52 and 70, 74 and 92, 70 and 100.

The diagnosis of perforated carcinoma of the stomach was made in only 5 cases,[27, 33, 40, 56, 62] and, of the remainder, fewer were diagnosed even as perforations

* Based on an analysis of 44 cases.

than as such varied conditions as appendicitis, peritonitis, cholecystitis, internal hæmorrhage, or simple carcinoma with perforation unsuspected. In one case aortic aneurysm was the provisional diagnosis.

Operation was performed in 24 of these fulminating cases, of whom 11 left hospital alive—an immediate operative mortality of 54 per cent. If we exclude the cases of gastrectomy whose high recovery rate is probably artificial (*see below*), the immediate mortality rate rises to 68 per cent. This same high mortality rate seems to hold, no matter how early operation is performed.

Perforation is through the anterior wall of the stomach in nearly nine-tenths of the cases. In only two cases was perforation multiple. In one case[37] perforation occurred through an acute ulcer proximal to an annular tumour, and once[17] perforation occurred through the anterior wall although the growth was on the posterior wall. The perforation is usually less than a $\frac{1}{4}$ in. in diameter, but in one-sixth of the cases it is larger than a penny piece. In the enormous majority of cases the perforating tumour lies near the pylorus or on the lesser curvature, and in 84 per cent it is of the ulcerative variety. Metastases are present at the time of the perforation in nearly half the cases—usually in the omental glands, but sometimes in the liver, the pancreas, or the portal vein.

The pathological appearances of peritonitis are nearly always present shortly after perforation, and the exudate becomes seropurulent usually within twelve hours; occasionally the peritoneal cavity remains dry and free from severe congestion for some hours after perforation. The peritoneal exudate is not infrequently described as brown or black in colour.

The malignancy of the perforating tumour was confirmed histologically in approximately one-half of the cases, and in these the adenocarcinoma was the commonest histological variety.

II. SILENT PERFORATION OF CANCER OF THE STOMACH INTO THE GENERAL PERITONEAL CAVITY *

This group includes one-third of all fully reported cases. The age and sex incidence corresponds to those of the fulminant variety. Only three of the silent cases had much pain, and even in these tenderness was slight or absent. The commonest course is an ascitic distension of the abdomen, with usually a dull generalized abdominal pain of gradual onset, and accompanied by little or no tenderness or rigidity. In one-fifth of the cases a palpable tumour is present. Occasionally[42, 52] the only signs of perforation are sudden pallor, anxiety of expression, a rise in pulse-rate, a fall in temperature, and some slight abdominal tenderness. So far as can be ascertained, nearly two-thirds of the silent cases perforated while the patients were in bed in hospital undergoing treatment for gastric symptoms.

Previous Indigestion is of less than a year's duration in nearly nine-tenths of the cases in this group, and only three reported cases of silent perforation give a dyspeptic history of more than a year. Previous hæmatemesis is more often present than absent. No free acid was found in the two cases whose test-meal was examined.

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* Based on an analysis of 23 cases.

In only one of these cases was perforation even suspected, although in many a diagnosis of carcinoma of the stomach had been previously established. Tuberculous peritonitis, malignant peritonitis, and internal hæmorrhage are the most common misdiagnoses. Operation was undertaken in less than half of the cases, with an immediate post-operative mortality of 67 per cent.

The latent perforation, just as the fulminant, is usually solitary, and through the anterior wall of the stomach, although multiple perforations and posterior perforations occasionally occur.[45, 55, 66] The perforating tumour is almost invariably found in the pyloric region or on the lesser curvature. The ulcerative variety of cancer predominates, but proliferative and annular tumours are more common in this than in the fulminant series. Metastases in the gastric glands, the liver, or the lungs are already present in nearly half the cases at the time of perforation. Histologically, the adenocarcinoma predominates.

The peritoneal exudate is frequently purulent at the time of death or of operation; the peritoneum rarely shows marked congestion, and sometimes[9, 42] death supervenes before any peritoneal reaction occurs.

THE OPERATIVE TREATMENT OF PERFORATED CARCINOMA OF THE STOMACH

Theoretically, the treatment of choice in cases of perforated carcinoma of the stomach would perhaps appear to be the same as that adopted in perforated gastric ulcer, namely immediate closure of the perforation with or without drainage of the peritoneal cavity, and perhaps supplemented by gastro-enterostomy, to be followed by gastrectomy (in cases of carcinoma) at a later date. This treatment was in one instance adopted,[20] to leave the patient still alive and well ten years later. The presence of irremovable metastases in one half the cases of perforated carcinoma, however, abolishes in these any hope of a radical cure. Further, varying local conditions have necessitated in the reported cases a variety of technique at the initial operation.

The chief hindrance to simple closure of the perforation is the difficulty of apposing its friable malignant edges by sutures, and this sometimes suggests immediate gastrectomy as the only practicable procedure. The seven cases in which this line of treatment was adopted all made at least an immediate recovery, but it must be remembered that gastrectomy would be performed only in cases with the most favourable possible general condition, and there is a tendency probably for solitary gastrectomy successes to be reported, and for gastrectomy failures to be absent from the literature.

The recorded results of the various immediate operative procedures are best summarized in a table:—

	Recovered	Died
Drainage alone	1	4
Closure alone	1	3
Closure and drainage	1	3
Local excision and closure ..	1	2
Closure and gastro-enterostomy	5	7
Closure and jejunostomy ..	–	2
Jejunostomy alone	–	1
Gastrectomy[10,28,41,61,62,63] ..	7	–
Total	16	22

PERFORATION IN 'ULCER-CANCER' AND IN PRIMARY CARCINOMA OF THE STOMACH *

It has been suggested that liability to perforation is a feature, and, indeed, an exclusive feature, of those cancers of the stomach which occur at the site of a previously existent simple gastric ulcer. This view is supported by the undisputed tendency of simple ulcer completely to destroy the muscular coat of the stomach, by the great preponderance (80 per cent) of ulcerating forms of carcinoma among perforated tumours, and by the perforating tumour's location, in 92 per cent of accurately reported cases, near the pylorus or at the lesser curvature. Of all perforated tumours, however, only 29 per cent complain of more than three years' previous indigestion, and 61 per cent have had dyspepsia of less than a year's duration: one case indeed,[28] in which a bismuth series six months before perforation failed to reveal any pathological lesion, establishes the occurrence of perforation in a recent cancer of a previously healthy stomach.

It is at this point convenient to make some effort to explain the occurrence of two separate varieties of malignant perforation of the stomach. We find that of the fulminant perforations only 46 per cent give a history of less than a year's indigestion, while 87 per cent of the silent perforations have had dyspepsia of this short duration. Further, of the eight fulminant cases whose gastric acidity was measured, while two had no free acid, one is stated to have had free acid present, one had free acid present in reduced amount, one had a normal free acid value, and three had definite hyperacidity. The two silent perforations whose test-meal had been examined both presented a low combined acid value, and an absence of free acid. This tendency of fulminating perforation to occur in cases with high gastric acidity and long history, of silent perforation to have a low acidity and a short history, at once suggests that the former may be a complication of ulcer-cancer, the latter a complication of primary carcinoma of the stomach.

The selection of cases of ulcer-cancer from a mass of published case reports is a difficult task—recognition of the condition is sufficiently puzzling and controversial when the whole clinical and pathological record of a case is directly accessible—yet in six of the reported cases (Friedenwald and McGlannan (2), Isch-Wall, Jaisson, Quenu, and Toms) a previous ulcer could be excluded by their short histories, their achlorhydria, and the lack of ulceration in the perforated tumour, perforation having in these cases presumably occurred from necrosis and sloughing of tumour tissue rather than from ulcerative destruction. Of these six cases, two[36, 66] had a relatively painless course, and one[56] had a painful onset but little tenderness. The remaining three cases[27, 34] had a painful course, but an early death (rapid even for a perforation) after two to five hours, from general peritonitis. The milder course in the first three of these is probably accounted for by the low acidity of the escaping gastric content, the rapidly fatal peritonitis in the second three cases by the admittedly septic content of many achlorhydric malignant stomachs.

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* The term 'primary carcinoma of the stomach' is in the remainder of this paper used as a convenient title for those cancers of the stomach which are not preceded by simple peptic ulceration.

As a contrast to these, five cases (Albertoni, Thiede, Suter, Reiser, and the third new case reported above) could be justifiably labelled ulcer-cancer from their high gastric acidity, long histories, and strong resemblance to simple ulcer in appearance—malignancy in these was suspected only because of metastases, or because of their subsequent course. (Three of them were definitely described as typical ulcer-cancers, but the difficulty of establishing a histological diagnosis of ulcer-cancer in a tumour whose muscle coat and muscularis mucosæ have been destroyed at the site of a perforation must be borne in mind.) All these cases pursued a course identical with that of a perforated peptic ulcer.

From these considerations it is perhaps justifiable to conclude that perforation of a primary carcinoma of the stomach is likely to be either relatively painless, mild, and gradual in its course, or, if sudden and painful, then rapidly fatal from septic peritonitis; it is certainly true that the symptoms of perforated cancer of the stomach will approximate closely to those of a typical perforated peptic ulcer, if the gastric acidity is high and the previous indigestion of long duration.

GENERAL PERITONITIS IN CANCER OF THE STOMACH WITHOUT PERFORATION

Perry and Shaw, in a detailed consideration of perforated cancer of the stomach, describe 17 cases of carcinoma of the stomach that died of peritonitis, but in whom no actual perforation of the stomach could be found after death. In 12 of the cases the onset of peritonitis was preceded by paracentesis or by an abdominal operation, but in the remaining 5 no such obvious route for infection was open. By permission of Professor John Fraser I append notes of a similar fatal case of carcinoma of the stomach, with acute peritonitis, but without perforation :—

A man, aged 46, complained of acute persistent boring epigastric pain, of sudden onset, and of twelve hours' duration. Green sour fluid had been vomited; several years of 'indigestion' had preceded this attack. The temperature was 100·8° and the pulse-rate 88; the whole abdomen was motionless and rigid; there was considerable general abdominal tenderness, but this was intense in the left upper abdomen. No free fluid was suspected, and the liver dullness was not reduced. On a diagnosis of perforated peptic ulcer laparotomy was performed, and the appearances of an acute peritonitis found. A large tumour mass was present in the pyloric part of the stomach, but no perforation was present. Fixity of the tumour and wide involvement of the omental glands prevented any attempt at gastrectomy, as also did the general condition of the patient. A drain was accordingly passed down to the neighbourhood of the tumour, and the wound closed. Death rapidly followed operation. At autopsy the removed stomach was distended with water without any leakage occurring through the tumour or through the stomach above it. The intestines were healthy and collapsed, the appendix was pale and free from disease, and no inflammatory focus was present elsewhere in the abdomen. Histologically the tumour was of undifferentiated spheroidal cells.

CONCLUSIONS

1. Two-thirds of the cases of perforated carcinoma of the stomach are fulminant in their course, closely resemble perforated peptic ulcer in their symptoms and signs, and should be diagnosed as perforations of the stomach. The only puzzling feature, present in one-fifth of the cases, is a relative or absolute absence of rigidity. An exact diagnosis of perforated carcinoma is only likely if the gastric tumour has been previously diagnosed.

2. In one-third of cases perforation is more or less silent, pain and abdominal rigidity being slight or absent. Perforation should be suspected in cases of rapid ascites or collapse when a history suggestive of gastric carcinoma can be elicited.

3. In both of these groups the perforating tumour is nearly always of the ulcerative variety, and situated on the lesser curvature or near the pylorus.

4. In nearly half of all cases metastases are already present when perforation occurs.

5. There is some evidence that a perforated ulcer-cancer of the stomach resembles in its symptoms and course a perforated peptic ulcer. Primary cancer of the stomach tends to perforate atypically, being either mild and gradual, or else causing early death in a few hours from septic peritonitis.

6. The immediate operative mortality rate closely approaches 60 per cent. Immediate gastrectomy has been practised successfully in seven cases; excluding gastrectomy, the most effective form of treatment appears to be closure of the perforation, supplemented by gastro-enterostomy, and followed later by gastrectomy, if removal is practicable.

7. Peritonitis can occur in the course of a case of cancer of the stomach without actual perforation of that organ.

I am indebted to Mr. J. M. Graham for permission to record the case which opens the present series, and which was treated in his wards. The other original cases were collected by Mr. L. B. Wevill and the Statistical Research Department of the Royal Infirmary, Edinburgh. I wish to express my indebtedness also to Mr. W. J. Stuart, Mr. J. W. Struthers, Professor John Fraser, Dr. Alexander Goodall, and Mr. K. Paterson Brown, for permission to use their cases.

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BILATERAL BIPARTITE PATELLÆ

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A PATELLA in two parts is of scientific interest as an anatomical rarity and of practical importance in the differential diagnosis of fracture. This communication records an instance in which the condition was met with in both patellæ of a male dissecting-room subject aged 63 years. The fact that attention is not directed to the condition in most of the recent standard text-books of orthopædic surgery warrants this brief article.

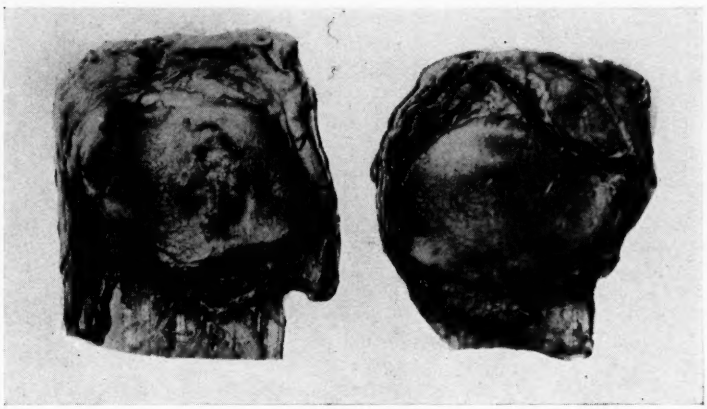

FIG. 382.—Posterior view of the patellæ. The supero-lateral portion of each patella is separate from the main portion. On the right side this separation has been made more evident by a knife-cut.

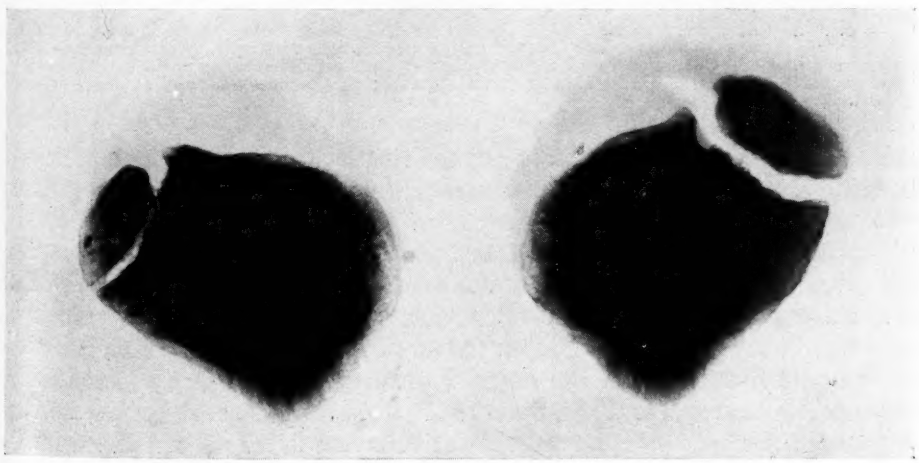

FIG. 383.—Radiogram of patellæ in *Fig.* 382. The fragment at each supero-lateral angle is seen to be a separate piece of bone.

The gross appearances of the right and left patellæ are similar. At the supero-lateral angle of each patella a separate fragment is to be seen. It is oval in shape, about 2·5 by 2 cm. in diameter, bony in structure, and separated from the main portion by a complete cleft (*Figs.* 382, 383). The slight differences between the two fragments are that the right one is a trifle larger and more on the superior border, while the left one is a little smaller and more on the lateral border. Both of them, it will be noted, include the supero-lateral angle.

A bipartite patella can be, theoretically, the result of either an ununited fracture or the failure of two ossification centres to fuse with each other. It was thought that a microscopic examination of this specimen might assist in deciding which mechanism accounted for this particular example of the condition, so sections were

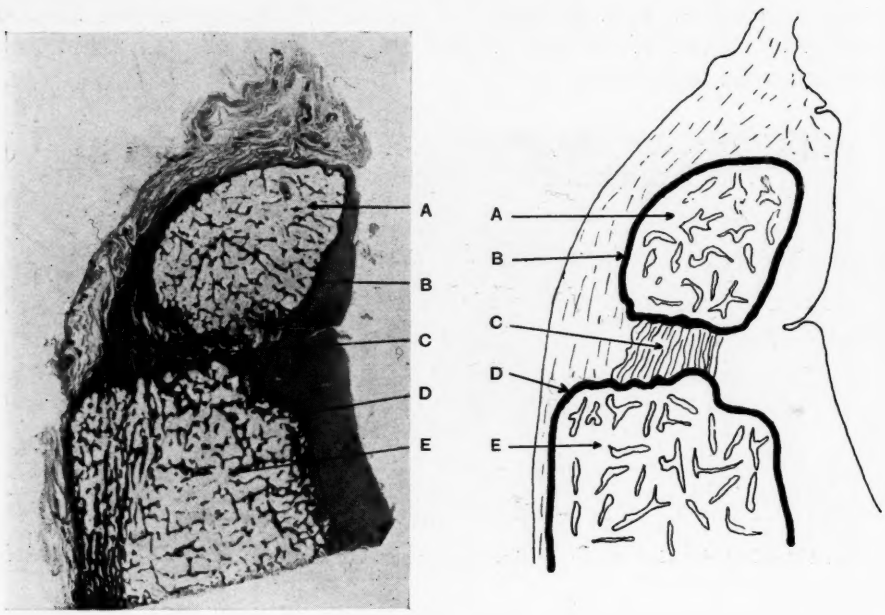

FIG. 384.—Low-power photomicrograph and key sketch of section through the cleft in the bipartite patella. The separate portion is above, and the posterior or articular surface of the patella to the right A, Cancellous bone of separate fragment of patella; B, Zone of old calcified cartilage; C, Fibro-cartilage bond of union; D, Zone of old calcified cartilage; E, Cancellous bone of main portion of patella. (× 2·6.)

cut through the two bony fragments and the tissue connecting them to each other. The sections were stained with hæmatoxylin and eosin, and certain points of interest were observed on examination (*Fig.* 384).

The first point of interest concerned the condition of the articular cartilage, which covered not only each fragment but also the tissue in the area between them. The articular cartilage was continuous and showed no evidence of the repair that could be expected if there had been a fracture of the patella. As each bony fragment offered a foundation for the articular cartilage and was firmly joined to it, it seems almost inconceivable that a fracture of the bone could have occurred without a complete coincident fracture of the articular cartilage. A small fissure was present in the articular cartilage over the area joining the two bony fragments, but this fissure did not extend through more than half the thickness of the articular

cartilage. There was no change in the deeper part of the articular cartilage in this area, and no substitution of connective tissue for cartilage in the area which would have represented the site of fracture in the cartilage if the patella had been fractured.

The second observation of interest derived from an examination of the slides was the histological picture in the gap between the bony portions. This gap was filled in with a type of connective tissue which demonstrated some of the features of both dense irregularly arranged fibrous connective tissue and cartilage. The fibrous element was the predominent feature of the matrix, but occasional groups of cells, in lacunæ and surrounded by cell envelopes, indicated a cartilaginous heritage. The bone was separated from this tissue by a line of demarcation similar to that surrounding the remainder of each bony portion. Such lines of demarcation are familiar to those who study bone, and they arise because other tissues, such as cartilage, never become bone but are always replaced by bone. Thus there is always a ' watermark ' where bone formation encroaches on any other tissue.

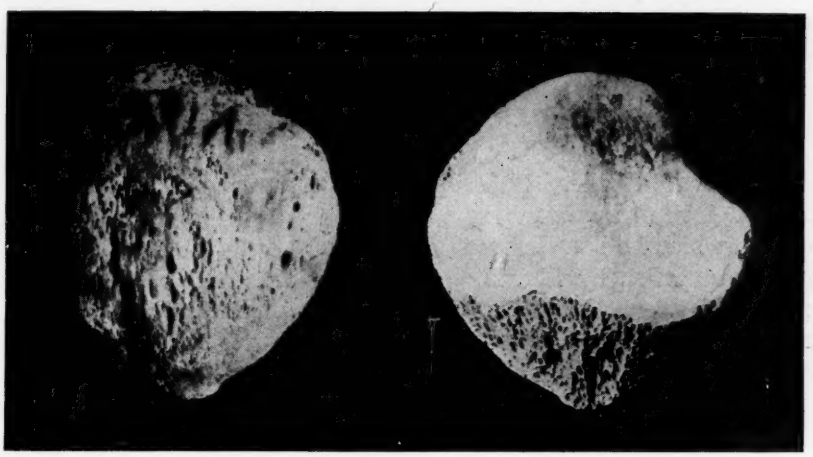

FIG. 385.—Though emargination of the patella appears not to have been described before 1902, its occurrence is no new thing, as this photograph of a specimen in Case 27 in the Natural History Museum at Torquay, England, exemplifies so excellently. This patella was found with several other prehistoric human bones beneath the upper stalagmite deposit in Kent's Cave near Torquay. It dates back probably to Magdalenian or Aurignacian times or earlier. For this photograph I am indebted to Professor J. C. Boileau Grant and to Mr. A. H. Ogilvie, F.R.A.I., the Curator of the Museum.

This watermark is often nothing more than a junction of two surfaces of different natures, a junction marked by the precipitation of stain. This phenomenon often suggests the presence of a cement substance between the two surfaces, so that the watermarks are on occasion, perhaps none too accurately, called ' cementing lines '. Lines of demarcation are intensified when bone replaces cartilage because the line is accentuated by the abrupt change in the staining reaction of the two types of matrix. When the formation of bone from an ossification centre has spread throughout an area formerly cartilaginous, the spread of ossification is marked by an ever-widening circle or line of demarcation between the cartilage and the bone.

Thus the picture in this area between the two bony portions of the patella suggests that the cause of the gap is the premature cessation of the spread of ossification from two separate centres. The complete line of demarcation around each bony portion certainly suggests this explanation for the bipartite condition,

but cannot be considered as absolute evidence for this conclusion because it is possible that an abortive attempt at repair of a fracture might produce a line of demarcation between each bony fragment and the tissue which occupied the area between them. If, however, the latter phenomenon had occurred, there would be, it is thought, a histological picture of much irregularity in outline with other evidences of attempted repair, rather than a picture not dissimilar to that seen around the remainder of the periphery of each bony fragment.

In a search for additional specimens of bipartite patella, 153 dried patellæ from our bone collection were examined. One of these had a furrow on the articular surface about 5 mm. from the lateral border. The area marked off by the furrow was penetrated on its anterior surface by a nutrient foramen, suggestive perhaps of an independent ossification centre. Seven other patellæ showed, in place of a supero-lateral angle, a depression first described by Kempson[7] under the name of "emargination". (*Fig.* 385.) The other patellæ were found free from defects of the borders and showed no sign of a bipartite character.

A bipartite character is not peculiar to the patella, but is found in other bones such as the parietal, zygoma, medial cuneiform, and sesamoid of the great toe. Boyd[2] recently reported a pair of bipartite carpal navicular bones.

HISTORICAL REVIEW

In 1883 Wenzel Gruber,[4] of St. Petersburg, described the first case of 'patella bipartita' and gave to the condition its name. He reported an autopsy on a man of 21 years in which he had demonstrated a patella, otherwise normal, with a small piece of bone attached by fibrous tissue to the supero-lateral angle. There the matter rested for nineteen years, until 1902, when Joachimstal[5] described a patella consisting of two bony parts, and Kempson[7] noted that a depression at the supero-lateral angle was a common variation.

In 1904 Wright[12] described an anomalous patella in which two accessory patellæ included the greater part of the lateral border of the bone.

In 1919 Salmond[9] described cases of fissured fracture of the patella in the neighbourhood of the insertion of the vastus lateralis. In the light of present knowledge there is little doubt that some of these cases were not fractures but anomalies of development.

In 1921 Wingate Todd and McCally[11] found some type of defect of the patellar border, such as fissure, fragmentation, or emargination, in 3 per cent of 682 skeletons. They explained all these conditions as phases of a single type of anomaly, that in which the patella is not ossified from a single centre but from two or more centres.

In 1925 George and Leonard[3] reported 6 cases of persons having a separate piece of bone at the supero-lateral angle of the patella, and in 5 the condition was bilateral.

In 1930 Kalies[6] reported the history and X-ray findings on 11 cases of bipartite patella. Ten had the separation at the supero-lateral angle and the eleventh was a very rare variety with a transverse cleft towards the distal part of the patella. The anomaly was unilateral in 4 of the 5 subjects in which X-rays were taken of both knees. In 1931 Neviaser[8] reported a single instance of a unilateral bipartite patella.

EXPLANATION OF THE OCCURRENCE

Bipartite patella is generally stated to be an anomaly of ossification. Ossification of the patella begins in the second year and is complete about puberty. Ossification is usually from a single centre and rarely from two or more centres.

Adams and Leonard[1] and also Neviaser[8] state that, even with two centres of ossification, the adult patella is usually one single bone unless fusion should fail to occur; in which case the result is bipartite patella.

Todd and McCally[11] suggested that an examination of the patellæ of children between the ages of 3 and 5 years might show more than one centre of ossification.

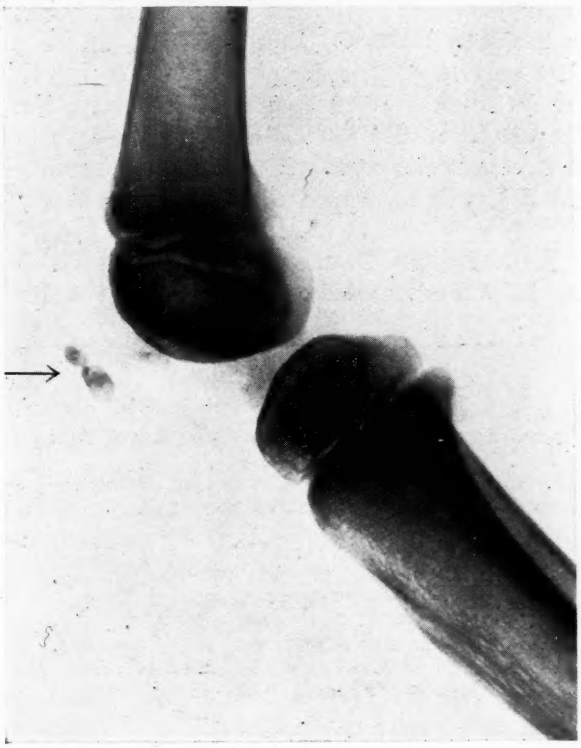

FIG. 386.—X-ray of the knee of a boy of 6½ years with two or three ossification centres for the patella, as indicated by an arrow.

This was done by Shands[10] in a study of the X-rays of the knees of 100 children between 2½ and 6 years of age. He found 2 children each with a patella having two definite centres of ossification. In one case the smaller centre was at the apex, in the other it was at the supero-lateral angle.

In following up this work of Shands, a study was made of the X-rays of 78 children's knees. None of these patellæ could be seen to be bipartite, but there is no record of the X-rays having been taken especially to give a clear patellar shadow, that is with the patella close against the film. One patella shows definite emargination at the supero-lateral angle. Another, from a boy of 6½ years, is of special interest (*Fig.* 386). It appears to have three centres of ossification, though

there may be really only a single centre from which ossification is spreading irregularly. A second X-ray from the same child at 11 years shows no sign of bipartitism. This indicates that the presence of multiple centres of ossification in the young child is not always followed by the development of bipartite patella when development is complete. That is to say, multiple centres of ossification precede, but do not necessarily produce, a bipartite condition.

SUMMARY

In bipartite patella it is with rare exceptions the supero-lateral angle that is separate from the main portion of the bone. This condition seems to be due to the failure of an accessory centre of ossification to unite with the main portion of the bone. Bipartitism is mostly bilateral. Emargination is an allied condition, differing not in kind but only in degree.

In addition to its interest as an anatomical curiosity, there is the practical point that bipartite patella should not be mistaken for a fracture. The location of the crack at the supero-lateral angle will arouse the surgeon's suspicion, and the finding of a similar defect in the opposite patella will probably confirm it.

To Professor J. C. Boileau Grant and Dr. Arthur W. Ham the author is greatly indebted for helpful advice and assistance in the preparation of this report.

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EXPERIMENTAL SURGERY

OSTEITIS FIBROSA: AN EXPERIMENTAL STUDY

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INTRODUCTION: BIOCHEMICAL CONSIDERATIONS

Until recent years the group of diseases classified clinically as the osseous dystrophies has remained outside the field of exact pathology. The group includes von Recklinghausen's osteitis fibrosa with cysts and giant-celled tumours, localized osteitis fibrosa which may be single or multiple, Paget's osteitis deformans, rickets, renal rickets, 'delayed' rickets, cœliac rickets, osteomalacia, and various idiopathic forms of osteoporosis. Although it is now generally recognized that each of these conditions has its own specific pathology, yet it must be remembered that they also have the common character of the decalcification of the skeleton. It is therefore by the study of the calcium metabolism in these different disorders that the mechanism of ossification and decalcification, both physiological and pathological, is being elucidated. Therefore, although the main object of this paper is to investigate the process by which hyperparathyroidism produces the bony lesions which have come to be recognized as characteristic of its action, it is necessary first to consider osteitis fibrosa in relation to the general metabolism of calcium.

The skeleton, besides being the framework of the body, is the reservoir of calcium for the organism, which is constantly being drained or built up, according to the supply of available calcium in the serum, and the mechanical requirements of the bones themselves.

Calcium differs from most other important metabolites, such as sugar or chloride ions, in that there is no conservation of it in the body, and deprivation of calcium results in a constant drain of it from the skeleton into the urine and fæces, in excess of the amount absorbed—a so-called negative calcium balance.

Lack of calcium may be due to an actual insufficiency in the diet, or to deficient absorption from the intestine in spite of an adequate diet, or may be the result of excessive excretion of calcium salts. Calcium can only be absorbed from the intestine in soluble form.[1] Excess of phosphate or alkali (carbonate) in the diet precipitates the calcium in the gut and prevents its absorption, while incomplete digestion and absorption of fats causes precipitation of calcium soaps in the intestine with the same result. Similarly, lack of vitamin D, which is necessary to the absorption of fats, causes insufficient absorption of calcium, and, as calcium salts tend to be adsorbed on to protein molecules, it may well be that incomplete protein absorption from the gut, by minimizing calcium absorption, is a factor in the etiology of 'idiopathic' forms of osteoporosis.

As in absorption, so in excretion, calcium is influenced by variations in the metabolism of other substances, the effects of which are reflected in the calcium content of the serum. The serum calcium must be regarded as a solution in 'biological saturation' with the calcium phosphate of the bones and is normally 9 to 11 mgrm. per 100 c.c. serum. This biological saturation is greatly in excess of the ordinary chemical solubility of calcium phosphate and is dependent on three factors: the concentrations of protein and of phosphate in the serum, and the amount of parathyroid hormone present.

Part of this excess calcium in the serum is due to adsorption of calcium salts on to the serum proteins. The amount adsorbed varies directly with the amount of protein present, 1 mgrm. of protein being equivalent to approximately 0·5 mgrm. of calcium per 100 c.c. serum, so that normally 2·5 to 4·5 mgrm. of the total serum calcium can be ascribed to this factor.[2] The adsorbed calcium, however, is not ionized and is physiologically inactive—for example, the reduction of the serum proteins which occurs in certain forms of nephritis, with consequent reduction of the adsorbed calcium, does not cause tetanic symptoms.

The remainder of the serum calcium is present as calcium ions formed by dissociation of the calcium phosphate of the bones, but the amount, 6 to 7 mgrm. per 100 c.c., is still in excess of the normal solubility of calcium phosphate, 2·5 mgrm. per 100 c.c. This excess in ionized calcium is due to the influence of the parathyroid hormone.[3] The mechanism of this action is not fully understood, but not only has it been shown that the ionized calcium of the serum is reduced after parathyroidectomy, and is restored by the administration of parathormone, but that hypercalcæmia can be produced by excess of parathormone, and that the degree of hypercalcæmia is proportional to the amount of parathormone given.

Although the dissociation of the calcium phosphate of the bones into calcium and phosphate ions of the serum is promoted in this way by the parathyroid hormone, the dissociated ions and the solid calcium phosphate of the bones are still in equilibrium. They are therefore subject to the law of ionic dissociation—namely, that the concentrations of the calcium and phosphate ions, if altered, must vary inversely with each other, in order that they may remain in equilibrium with the undissociated calcium phosphate.[4] Consequently, excess of phosphate ions in the serum from other sources causes a fall in the serum calcium, with deposition of calcium phosphate in the bones, while a reduction of phosphate in the serum is accompanied by a rise in serum calcium, and solution of calcium phosphate from the bones.

Only this ionized part of the calcium in the serum is physiologically active, and reduction of the ionized calcium by parathyroidectomy or by excess of phosphate ions will cause the symptoms of tetany to appear. (In forms of nephritis other than those referred to above, where phosphate is retained in the serum, the concentration of calcium ions may be reduced to such an extent as to cause tetany.)

It must be noted that although the protein-adsorbed calcium is inactive, it is necessary to determine the proportion of the total serum calcium thus put out of action in any particular case, before it is possible to estimate the amount of active calcium present. In the investigation of a case of osteoporosis, therefore, the significance of an abnormal serum calcium can only be interpreted by a knowledge of the serum proteins and phosphate.

There are thus two main factors which control the balance of calcium between the serum and the bones, the concentrations of phosphate ions and of parathormone

in the circulation. Turning first to the influence and variations of the phosphate, we find ourselves dealing at once with the acid-base metabolism of the body, because the phosphate radical is one of the most important 'buffer ions' in the tissues. If acidosis is impending, the buffer phosphate is excreted and the serum phosphate falls; calcium phosphate is then dissolved from the bones to restore ionic equilibrium in the serum, and the consequent excess of calcium in the blood is excreted by the kidney. Thus acidosis, which occurs in so many conditions, may result directly in a drain of calcium from the skeleton into the urine. (A distinction must be made between the acids present in the gut which are necessary to the normal absorption of calcium, and the acidosis produced by faulty metabolism, which may cause decalcification of the skeleton.)

Calcium metabolism, then, is dependent on many outside conditions and circumstances—acidosis with all its causes, the metabolism of fat and protein, vitamin D effects, and errors of dietary. All these finally affect the calcium reserves of the body, and to them the decalcification of the skeleton observed in many clinical cases, can be directly attributed. In rickets and cœliac rickets the skeletal effect is due entirely to lack of calcium in the serum; in renal rickets it is due to phosphate retention by the kidney, with consequent excretion of calcium phosphate by the gut (*see Case* 1, p. 585), while osteomalacia is the combined result of diminished absorption of calcium following vitamin lack, and the acidosis of malnutrition and a cereal diet, together with the extra drain on the calcium reserves by the fœtus in utero.

All cases of decalcification cannot, however, be explained by these phenomena alone. Two advances have been made in recent years which have gone far to the elucidation of the problem—the discovery of phosphatase by Robison in 1924,[5] and the preparation of an active extract of the parathyroid glands by Collip in 1925[6]. The discovery of parathormone has placed in our hands not only the explanation of the apparent supersaturation of calcium in the serum, but also has helped us to recognize that now familiar type of von Recklinghausen's disease consequent on a parathyroid adenoma. It is to be noted, however, that decalcification by parathormone proceeds by the same mechanism as by acidosis. Thus Albright, Bauer, and their colleagues[7] have shown that the first action of parathormone is to sweep phosphate from the blood into the urine; the serum phosphate falls, consequently the serum calcium rises, and reserves of calcium and phosphate are mobilized from the bones. The excess of calcium is excreted by the kidney, more is supplied from the bones, and so a drain of calcium from the skeleton into the urine is established. Decalcification, therefore, whether by parathormone or acidosis, is the result of excretion of phosphate. The difference, however, between the two agents is that in the case of parathormone there is also an *absolute* hypercalcæmia, due to the increase in solubility of the calcium phosphate in the bones, while in acidosis the calcium in the serum is only increased relatively to the phosphate.

Fatal doses of parathormone result in an increase of phosphate as well as calcium in the serum shortly before death, so that parathormone may have a direct action on the calcium of the bones in these circumstances: this action, however, does not come into play with other than lethal doses. Toxic doses cause weakness, hypotonia of the muscles, and anorexia, followed by vomiting, coma, and death. The apparent toxicity, however, varies with the amount of calcium in the diet, and much larger doses of parathormone can be tolerated by an animal on a low calcium diet, where the hypercalcæmia is not so extreme, than by an animal on a high calcium

diet.[8] The toxic element is, therefore, the hypercalcæmia rather than the parathormone—a point of some importance in connection with the experimental results in this paper.

In the human subject there can be no doubt that the hyperparathyroidism consequent on a parathyroid adenoma does cause von Recklinghausen's disease, and it has been repeatedly shown that removal of the adenoma causes the bones to return gradually to normal. However, not all parathyroid tumours have von Recklinghausen's disease—40 per cent of the cases of parathyroid adenomata collected by Barr and Bulger[9] had no bony lesion. Further, many cases of generalized osteitis fibrosa established by histological examination of a piece of bone removed for section have shown, on biochemical investigation, no evidence of hyperparathyroidism. In not a few such cases a thorough exploration of the neck has failed to demonstrate a tumour, and even normal parathyroids have been removed without effect on the bones. Also we have seen that the skeleton is liable to decalcification by such conditions as acidosis, in the same way as by parathormone, at any rate in ordinary doses. Considering all these facts, it is essential at the present stage of our knowledge not to regard the histological features of von Recklinghausen's disease and hyperparathyroidism as specifically related. The characteristic features of von Recklinghausen's disease are, clinically, that it is seen in fairly young adults, although the process actually began at some time in youth when the bones were most plastic; while, histologically, the presence of the cysts and the giant-celled tumours distinguish it from other decalcifying diseases. The question is: Are these histological characters necessarily the result of the action of parathormone, or can it produce decalcification without them? Conversely, can giant-celled tumours and cysts appear with decalcification from some other cause than hyperparathyroidism? Can von Recklinghausen's disease, complete with giant-celled tumours and cysts, be produced experimentally by the action of parathormone alone? The second part of the experimental work of this investigation is concerned with this problem.

The other discovery, that of phosphatase, has helped us to understand the chemical processes of ossification. Phosphatase is an enzyme that hydrolyses organic phosphates into inorganic phosphates, and it occurs at the three principal sites of phosphate metabolism—namely, in the intestinal mucosa where phosphorus is absorbed, in the bones where it is stored, and in the kidneys where it is excreted. The enzyme, however, is only present in these tissues when and where they are actively functioning. There is practically no phosphatase is the fœtal kidney, and the phosphatase of bone occurs only at the sites of active ossification,[10] at the epiphysial line and under the periosteum. It appears, in fact, to be produced by, or concentrated in, the osteoblasts in these situations. It is this local concentration of phosphatase in the osteoblasts that determines ossification; ionized inorganic phosphate is produced *in situ* from the practically non-ionized organic phosphates of the serum. This local increased concentration of phosphate ions upsets the local calcium-phosphate equilibrium, so that the solid salt is precipitated around the osteoblast. In old compact bone with widely separated bone-cells the calcium is precipitated in lamellæ round the osteoblasts; but in an area of newly forming bone with young osteoblasts crowded together, the calcium is precipitated as a network of fine fibrils in the tissue matrix. This physiological process of calcification to form bone is quite different from the process of pathological calcification,

such as occurs in tuberculous glands or arterial walls. The latter type of calcification is always preceded by *degeneration* of the tissue cells as the result of local toxins and/or local oxygen deficiency. The lipoid substances liberated in the process of degeneration form compounds analogous to calcium soaps, which gradually change into deposits of phosphate and carbonate of calcium.

This is the explanation of the metastatic calcification observed in experimental hyperparathyroidism, where toxic doses of parathormone have been given.[11] This metastatic calcification has clouded the conception of calcium mobilization by parathormone, for apparently excess of parathormone in the circulation causes actual deposition of calcium in the soft tissues. The toxic effects of hypercalcæmia mentioned above have, however, been observed by many workers, and McJunkin[12] has shown that the metastatic calcification in the soft tissues is always preceded by marked degenerative changes. This effect, then, is an example of pathological calcification, the calcium being precipitated from the serum, primarily in combination with lipoid bodies, independently of the presence or absence of parathormone.

It is the phosphatase in the osteoblast, then, that brings about ossification. Now it has been discovered that in von Recklinghausen's disease and Paget's disease and other disorders with extensive decalcification of the bones, there is a marked increase in the concentration of phosphatase in the plasma.[13] Normally the concentration in the plasma is very low, 0·06 units per cubic centimetre, but in these generalized diseases of bone the concentration of phosphatase in the plasma may be increased as much as twenty times or more. The questions arise: What is the explanation of this raised plasma phosphatase? Is it connected with the cause or the result of the disease process in the bones? What is the function and fate of the phosphatase in this high concentration in the blood? Is it destroyed or excreted? The first part of the experimental work set out below deals with these problems.

EXPERIMENTAL WORK

PART I.—EXPERIMENTS WITH PHOSPHATASE

Preparation.—A sterile solution of phosphatase, suitable for injection into rabbits, was made by a modification of Kay's method as follows: Two warm fresh kidneys enclosed in the perinephric fat, to avoid bacterial contamination, were obtained from a recently killed pig; the organs were dissected out from the fat with sterile instruments, and the renal capsules removed. The sterile kidneys were then dissected so that the cortex was roughly separated from the medulla (the phosphatase occurs almost exclusively in the cortex of the kidney, which is also much more easily crushed than the whole kidney with its fibrous calices). The cortex was then thoroughly ground up with sterile sand and chloroform water in a sterile mortar, and allowed to stand for twenty-four hours with repeated stirrings at room temperature. At the end of this time the fluid extract, containing about 90 per cent of the total phosphatase of the kidney substance, was collected and kept in an ice-chest, and subsequently was used for injection into the rabbits.

Estimation: Diminution of Activity on Keeping.—Kay's method and unit were also adopted—namely, a known quantity of solution containing the

unknown amount of enzyme was allowed to act on a substrate of excess of sodium-B-glycero-phosphate at a P_H of 7·6 for forty-eight hours at 38°C. The concentration of phosphatase was then calculated from the amount of inorganic phosphate liberated from the organic combination by the action of the enzyme, and the unit was expressed as that amount of phosphatase which, acting on excess of substrate under the above conditions, liberated 1 mgrm. of inorganic phosphate in forty-eight hours.

In all, three solutions of phosphatase were prepared during the course of the work, and it became necessary to estimate the strength of the solutions from time to time in order to determine dosage. The strength of the first solution was 20 units per cubic centimetre when first made, and *Fig.* 387 shows the rate at which the activity diminished over a period of seven months at — 4° C.

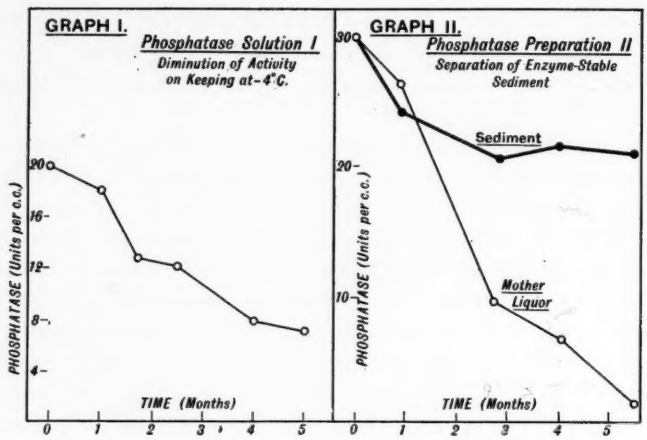

FIG. 387.

FIG. 388.

The second preparation of the enzyme was made some time later. It was richer in phosphatase (30 units per cubic centimetre) and it was found that on standing for a long time at — 4° C. a whitish sediment very slowly separated out. On investigation it was discovered that while the phosphatase activity of the mother liquor gradually diminished, that of the sediment remained constant. The precipitate was, in fact, a stable preparation of phosphatase. *Fig.* 388 illustrates the relative activities of liquor and sediment with the lapse of time.

Further investigation was instituted on this property of the kidney extract. It was found that the sediment could not be extracted from the fresh preparation by ordinary centrifuging or by filtering under pressure. However, on centrifuging at 30,000 revolutions per minute in a Sharple's centrifuge, a greyish-white substance gradually adhered to the sides of the vessel. This glutinous material was scraped off with a little distilled water and the resulting emulsion was found to be an extremely concentrated preparation of phosphatase, as much as 36 units per cubic centimetre. The chemical nature of the sediment was not exactly determined, but it gave the qualitative tests for protein. The enzyme was probably adsorbed on to the protein debris of the crushed renal cells.

Injection of Phosphatase into Rabbits.—The standard enzyme solution prepared, it was injected into rabbits to determine whether the plasma phosphatase could be raised by this means, and, if so, whether any lesion in the bones would

follow. The object of this procedure was to determine whether the high plasma phosphatase observed in decalcifying diseases is concerned with the causation of the condition, or whether it is a secondary result of the disease process.

Experiment 1.—Two adult rabbits on an adequate calcium diet were X-rayed, with controls, and their blood calcium, phosphorus, and phosphatase were determined. They were then given daily injections of the first solution of phosphatase, in increasing doses up to 65 units intramuscularly. Neither animal died as a result of this, and estimations of the serum calcium, phosphorus, and phosphatase were made at intervals for six weeks. At the end of that time, little effect having been noticed either in the blood chemistry or X-ray appearances, the method of administration was changed to the intravenous route, whereupon one animal died, and the other was injected with smaller doses for eight days more, and was then killed.

Table I shows the dosage of phosphatase, and the values of the serum calcium and the plasma phosphorus and phosphatase, the two sets of figures referring to the different rabbits.

Table I

Date and Calculated Units of Phosphatase Injected	Serum Calcium	Serum Phosphorus	Plasma Phosphatase
	Mgrm. per 100 c.c.	Mgrm. per 100 c.c.	Units per c.c.
April 19	R_1 14·4	4·4	0·16
	R_2 14·8	4·9	0·16
Increasing daily dose up to 65 units intramuscularly			
April 30	R_1 15·0	5·2	0·16
	R_2 14·2	5·0	0·14
Daily dose of 6 c.c. extract—equivalent to 62 units, falling to 47 units of phosphatase			
May 31	R_1 13·8	5·4	0·14
	R_2 15·2	4·8	0·19
Rabbits X-rayed. Intravenous dose up to 15 units daily			
June 8	R_1 13·6	3·8	0·14
	R_2 died		

It will be seen that the injections caused no effect on the serum calcium or phosphorus outside the normal variations for the rabbit, nor was the phosphatase itself raised in the plasma. Post-mortem examination showed some suppuration at the site of injection, but no softening of the bones or calcification of the viscera, which were normal in all respects. Sections were cut of the ribs, femur, and tibia, but showed no alteration from the normal bone histology.

Apart from the lack of bone change, it seemed extraordinary that the level of phosphatase in the plasma should remain normal, in spite of continued injection of the enzyme. Therefore it was decided to inject much larger doses in further rabbits, using the second stronger preparation of phosphatase, to see whether or not it was possible to raise the plasma phosphatase in this way.

Experiment 2.—After preliminary chemical investigation of two rabbits as before, 10 c.c. of emulsion of the phosphatase sediment, equivalent to 200 units,

were given intramuscularly daily for five days. Estimations were made of the blood calcium, phosphorus, and phosphatase on the second and fifth days, the blood being taken five hours after the last injection. Again (*Table II*) only very slight alterations in values were found, and as before no pathological effect was discovered in the soft tissues or decalcification in the bones.

Table II

	Serum Calcium	Serum Phosphorus	Plasma Phosphatase
	Mgrm. per 100 c.c.	Mgrm. per 100 c.c.	Units per c.c.
Before injection ..	R_1 16·0	4·4	0·12
	R_2 15·5	5·0	0·14
200 units of phosphatase injected daily			
2nd day	R_1 15·8	4·8	0·15
	R_2 15·5	5·4	0·16
5th day	R_1 16·2	4·8	0·14
	R_2 15·8	5·0	0·14

The negative results of these two experiments raised the question whether phosphatase prepared from a pig's kidney was active in a rabbit, and, if so, what was the reason for the rapid disapparance of such large amounts so soon after injection. The third experiment was therefore made to discover the fate of the phosphatase injected, whether excreted in the urine, or destroyed in the circulation. It was first necessary to estimate the phosphatase content of the urine. In the human this is a very difficult matter, because the large amount of inorganic phosphate present renders the extra amount produced by the phosphatase insignificant in comparison, the difference being well within the limits of experimental error. M. C. Bourne,[14] however, has reported that rabbits on a diet of cabbage only, excrete practically no phosphate in the urine. This point was investigated, and it was found that rabbits fed on a daily diet of 150 grm. of cabbage and 75 grm. of oats excreted only a minute amount of phosphorus in the urine. Consequently, it was possible to apply the ordinary technique to the estimation of phosphatase in the rabbits' urine.

Next it was necessary to determine whether phosphatase in the urine was stable, or whether its activity was in any way inhibited. To decide this point, the following experiment was performed :—

A series of five flasks was prepared containing: (1) Normal rabbit's urine; (2) Concentrated phosphatase solution; (3) Diluted phosphatase solution (1-10); (4) A mixture of 1 and 2; (5) A mixture of 1 and 3. Phosphatase estimations were performed on these five solutions, at intervals up to twenty-four hours later, and the results are set out in *Table III*.

From *Table III* the following facts can be deduced: (1) That phosphatase is normally excreted in small amounts in the urine (column 1). (2) That on standing this phosphatase is fairly stable in the urine (column 1). (3) That although the activity of the concentrated solution of phosphatase in urine, as in water, does decrease slightly on standing, the dilute solution is relatively stable (column 5). As the phosphatase in the urine of the rabbits in the main experiment which follows

is dilute, the results obtained may be regarded as accurate. (4) That the activity of phosphatase is not inhibited by the urine, as the phosphatase values in column 4 are roughly the means of columns 1 and 2, and those in column 5 are the means of

Table III

Hours after Mixing Urine and Phosphatase	Phosphatase Values (Units per c.c.)				
	(1) Rabbits' Urine	(2) Phosphatase Solution Conc.	(3) Phosphatase Solution Dilute	(4) Mixture of 1 and 2	(5) Mixture of 1 and 3
0	0·20	0·74	0·19	0·57 *0·47*	0·27 *0·20*
1½	0·19	0·71	0·18	0·55 *0·48*	0·24 *0·19*
7	0·22	0·55	0·19	0·51 *0·39*	0·27 *0·21*
24	0·18	0·61	–	0·46 *0·40*	–

The italic figures in columns 4 and 5 are the calculated arithmetic means of the phosphatase values of columns 1 and 2 and 1 and 3 respectively, for comparison with the phosphatase values in the mixtures of urine and phosphatase solutions actually found.

columns 1 and 3. The constant slight excess of the figures in columns 4 and 5 over the calculated amounts is due to the relatively increased activity of the enzyme by the dilution of the phosphatase solution with the urine (compare columns 2 and 3). This property is common to all enzymes.

Experiment 3. *Fate of Injected Phosphatase in the Body.*—An adult rabbit, fed on the same diet as in the preceding experiment, was put in a metabolism cage.

Table IV

Time	Plasma Phosphatase	Plasma Phosphorus	Urine Phosphatase	Urine Phosphorus	Volume Urine in Period
	Units per c.c.	Mgrm. per 100 c.c.	Units per c.c.	Mgrm. per c.c.	c.c.
9.50 a.m.	0·047	3·2	–	–	–
10.50 a.m.	–	–	0·263	0·55	3
11.0 a.m.	Injection of 580 units of phosphatase				
11.35 a.m.	**0·061**	–	–	–	–
12.35 p.m.	–	–	0·342	0·52	4
1.0 p.m.	**0·070**	**4·6**	–	–	–
1.30 p.m.	–	–	0·098	0·26	23
2.15 p.m.	–	–	0·160	0·48	6·5
2.35 p.m.	**0·054**	–	–	–	–
5.0 p.m.	**0·039**	4·0	0·132	0·56	11·5
9.40 p.m.	0·048	2·8	0·142	0·56	24
9.40 a.m.	0·055	2·8	0·095	0·46	64

After emptying the bladder, phosphorus and phosphatase estimations were made on the urine, and on a sample of blood taken from the ear. A massive single dose of 580 units of phosphatase (Sharple's centrifuge preparation) was then injected

intramuscularly at four different places. From an hour to an hour and a half later, the animal looked ill and had occasional tremors, but subsequently recovered. Specimens of blood were taken at intervals for the next twenty-four hours, and the urine collected at the same times. Estimations of phosphorus and phosphatase were made on both blood and urine, and the volume of urine in each period was measured. The results are shown in *Table IV*, and from these data the actual amounts of phosphorus and phosphatase excreted in the urine in each period were calculated and set out in *Table V* (columns 2 and 3). From these figures and the duration of each

Table V

Period	Total Phosphatase Excreted during Period	Total Phosphorus Excreted during Period	Rate of Excretion of Phosphatase	Rate of Excretion of Phosphorus
			Units per hour	Mgrm. per hour
9.50–10.30 a.m.	0·79	1·65	0·79	1·65
Injection of 580 units of phosphatase				
10.50–12.35 a.m.	1·37	2·08	**0·79**	**1·2**
12.35– 1.30 p.m.	2·25	6·0	**2·45**	**6·5**
1.30– 2.15 p.m.	1·04	3·12	**1·39**	**4·2**
2.15– 5.0 p.m.	1·52	6·49	**0·55**	**2·4**
5.0 – 9.40 p.m.	3·41	13·52	**0·73**	2·9
9.40 p.m.– 9.40 a.m.	6·10	29·20	0·51	2·4

Twenty-four-hour total of phosphatase excreted = 16·4 units (as against 580 units injected). (= Summation of Column 2.)

period, the *rates* of excretion of the two substances were calculated (columns 4 and 5, *Table V*). *Figs.* 389, 390 were constructed from the data in *Tables IV* and *V* and show respectively the plasma values and the rates of excretion of phosphatase and phosphate during the twenty-four hours after the injection. From *Fig.* 389

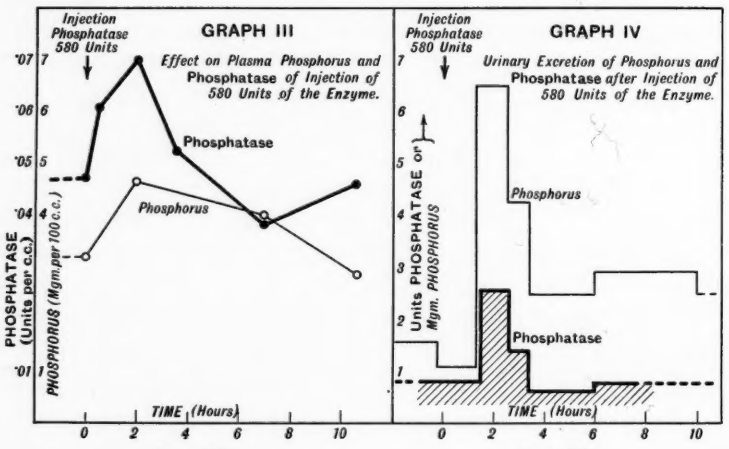
Injection Phosphatase 580 Units
GRAPH III
Effect on Plasma Phosphorus and Phosphatase of Injection of 580 Units of the Enzyme.
Phosphatase
Phosphorus
PHOSPHATASE (Units per c.c.)
PHOSPHORUS (Mgm. per 100 c.c.)
TIME (Hours)
Injection Phosphatase 580 Units
GRAPH IV
Urinary Excretion of Phosphorus and Phosphatase after Injection of 580 Units of the Enzyme.
Phosphorus
Phosphatase
Units PHOSPHATASE or Mgm. PHOSPHORUS
TIME (Hours)

FIG. 389. FIG. 390.

it can be seen that the plasma phosphatase is at a maximum two hours after the injection, presumably the height of absorption into the circulation, and that it falls to normal again three hours later. The corresponding rise in plasma phosphorus and the coincident increased excretion of phosphate (*Fig.* 390) indicate that while

the phosphatase is in the tissues it is actively producing inorganic phosphate from organic combination. In other words, phosphatase prepared from a pig's kidney *is* active in a rabbit.

The tremors (? incipient tetany) observed in the rabbit an hour and a half after the injection also correspond to the rise in plasma phosphorus at this time, and may possibly be due to a lowered serum calcium attendant on this. Unfortunately calcium estimations were not done in this experiment.

The rapid return of the plasma phosphatase to normal after its temporary rise explains the inability to find a raised plasma phosphatase in the first two experiments, as blood samples were taken five hours or more after the injections of the enzyme.

Fig. 390 shows a delay of one and a half hours in the excretion of phosphatase, after its rise in the plasma, followed by a period of two hours of increased excretion, after which excretion also returned to the normal rate. A consideration of *Table V*, however, shows that the actual total amount of phosphatase excreted in the twenty-four hours after the injection was only 16·4 units, whereas 580 units were injected. By far the greater proportion of the injected phosphatase must therefore have been destroyed in the body.

Summary of Results of Phosphatase Experiments

1. Phosphatase is normally excreted into the urine in small amounts.
2. Phosphatase prepared from a pig's kidney is active when injected into a rabbit.
3. Phosphatase injected into a rabbit over a long period of time produces no bony lesion.
4. Phosphatase injected in large doses produces only a transient change in the plasma level.
5. Phosphatase in excess of the normal is very rapidly destroyed in the body, only a very small amount being excreted.

The significance of these findings, and their bearing on the problem of the high plasma phosphatase in osteitis fibrosa, will be left to the main discussion following the second part of the experimental work.

PART II.—EXPERIMENTS WITH PARATHORMONE

The first experiment was undertaken to confirm some results obtained by Jaffe and Bodansky[15] in New York. By injecting quite small doses of parathormone, these workers were able to produce decalcification of the bones of young dogs, of such a degree as to cause deformities and fractures. Histologically, the bones showed many of the appearances of human osteitis fibrosa, such as fibrosis of the marrow, increased osteoclastic activity, and the formation of osteoid tissue, but they were unable to observe any bone cysts or giant-celled tumours. It was decided to repeat this experiment on rabbits and to study in greater detail the histological changes produced in the bones.

Experiment 4.—Four adult rabbits were kept on an ordinary diet of greens, oats, and bran, containing an adequate supply of calcium. The calcium, phosphorus, and phosphatase in the blood were determined, and controlled standard radiograms were taken of the bones. They were then each given daily 20 units

of parathormone intramuscularly. During the course of injections, further X-rays were taken, and blood chemical examinations were made at intervals, the results of which are shown in *Table VI.*

Table VI

Date and Dosage	Rabbit No.	Blood		
		Serum Calcium	Serum Phosphorus	Plasma Phosphatase
		Mgrm. per 100 c.c.	Mgrm. per 100 c.c.	Units per c.c.
May 17	1	14·6	4·6	0·050
	2	12·6	3·5	0·060
	3	11·6	4·4	0·050
	4	15·0	3·5	0·070
20 units of parathormone daily for 14 days				
June 2*	1	14·2	4·8	0·050
	2	13·8	3·6	0·055
	3	14·0	5·0	0·046
	4	13·5	4·2	0·066
Rabbits 3 and 4: 40 units of parathormone daily for 14 days				
June 16	3	14·2	3·9	–
	4	13·8	4·0	–
80 units of parathormone daily for 67 days				
June 15	3	12·9	4·7	–
	–	14·1	4·0	–
Aug. 22†	3	13·3	4·6	0·070
	4	14·5	3·7	0·075

* Rabbits 1 and 2 killed. † Rabbits 3 and 4 killed.

After fourteen days' treatment it was found that no effect was being produced on the serum calcium, phosphorus, and phosphatase, or on the bones, as far as could be determined radiographically. Two of the rabbits were killed and post-mortem examinations made. The bones showed no macroscopic evidence of decalcification, nor were any pathological changes found in the viscera or parathyroid glands. The bones were put in Zenker's fixative for section later, but meanwhile the dosage of parathormone for the remaining two rabbits was increased to 40 uints per day. After another fourteen days, blood examinations still revealed no change, so the dose was further increased to 80 units, an amount far in excess of that used by Jaffe and Bodansky. The injections were continued altogether for a period of three months without apparent effect, after which the two remaining rabbits were killed. Post-mortem examination again showed no obvious change in the skeleton or the viscera. The thyroid and parathyroids appeared normal, but in each rabbit a congested lymph-gland was found on each side of the neck. These, together with two of the ribs and a femur, were prepared for section. The lymph-glands showed hæmorrhages and mild inflammatory changes, but the thyroid and parathyroids presented a normal histology. The ribs and femora showed neither decalcification nor increased osteoclastic or osteoblastic activity, and the marrow was unchanged.

The absence of any of the changes reported by Jaffe and Bodansky in puppies given only a small fraction of the amount of parathormone that was given to the adult rabbits in this experiment was striking. It was decided to investigate younger rabbits on a low calcium diet, and to examine not only the serum, but to follow

the excretion of calcium and phosphorus in the urine and fæces as well. In addition, it was arranged to examine the bones histologically during the course of the experiment as well as post mortem.

A consideration of Sherman's[16] food analysis tables showed that the articles of food lowest in calcium, suitable for rabbits, were rice and tomato. In view of the variability of foodstuffs produced in different localities, an analysis was made of these two foods, and also of cabbage and oats in preparation for the third experiment using a high calcium diet. Some differences were found between the results obtained and the figures given by Sherman; both sets of figures are set out in *Table VII.*

Table VII

	Calcium grm. per 100 grm.		Phosphorus grm. per 100 grm.	
	Author's Result	Sherman's Figures	Author's Result	Sherman's Figures
Rice ..	0·012	0·009	0·083	0·096
Tomato ..	0·018	0·011	0·031	0·026
Oats ..	0·050	0·069	0·296	0·392
Cabbage ..	0·105	0·106	0·067	0·099

Experiment 5.—Two young rabbits 8 weeks old were put on a low calcium diet, consisting of 100 grm. of rice and 50 grm. of tomato daily. This was equivalent to an intake of 21 mgrm. of calcium and 114 mgrm. of phosphorus per diem, and a drop of radiostoleum was occasionally added to prevent rachitic changes.

After two months on this diet the animals had put on very little weight and their bones were very thin, but otherwise they appeared to be in an ordinary state of health. They were then transferred to a metabolism cage, constructed so that the fæces remained on the grid which formed the floor of the animal chamber, while the urine passed through and was collected in a receiver underneath the funnel-shaped bottom of the cage. Some difficulty was at first encountered with the zinc from the cage washings in the urine, as this metal tended to interfere with the calcium estimations. The difficulty was overcome by a slight modification in technique, and by coating the interior of the cage with hard wax.

The excreta were divided into four-day periods, and the total weight of fæces and volume of urine for each period were measured. Aliquot parts of fæces and urine were ashed in platinum crucibles, and the ash was extracted with 5 per cent HCl. The calcium in the extract was determined by the oxalate precipitation method, and the phosphorus by the method of Fiske and Subarrow.[17] In this way the total intake and excretion of calcium and phosphorus could be determined, and the effect of the parathormone on the balance of these elements watched. On the low calcium and phosphorus diet, the balances were both found to be negative, while the serum calcium was 10·8 mgrm. per 100 c.c., and the serum phosphorus 3·6 mgrm. per 100 c.c. Before injection of parathormone was commenced a portion of rib was resected from each rabbit, as the histological control specimen. The operation was done under local novocain anæsthesia with a cloth over the animal's head, and caused no pain or distress, the rabbit lying quietly without

struggling. Ribs were selected for this procedure, partly on account of convenience and ability to repeat the operation a number of times, and partly because Jaffe and Bodansky found the histological changes in the rib much more marked than in the long bones.

A course of injections of parathormone was now begun, with increasing doses for each four-day metabolism period, rising from 20 units to 160 units per diem.

Table VIII

Daily Dosage of Parathormone Units, 4-day Periods	Calcium			Phosphorus			Intake
	Serum	Daily Excretion Urine	Daily Excretion Fæces	Serum	Daily Excretion Urine	Daily Excretion Fæces	
	Mgrm. per 100 c.c.	Mgrm.	Mgrm.	Mgrm. per 100 c.c.	Mgrm.	Mgrm.	
0	10·8	37	27	3·6	130	40	Calcium, 21 mgrm. per day
20	–	**110**	**78**	–	**238**	**81**	
40	**12·2**	**130**	13	3·6	155	24	Phosphorus, 114 mgrm. per day
80	–	77	10	–	123	28	
160	10·3	63	12	–	184	16	

On the eighth day of injection, dosage being now 40 units, a sample of blood was taken and a second rib resected. The blood calcium had risen to 12·2 mgrm., while the phosphorus was still 3·6 mgrm. per 100 c.c. On the sixteenth day, after

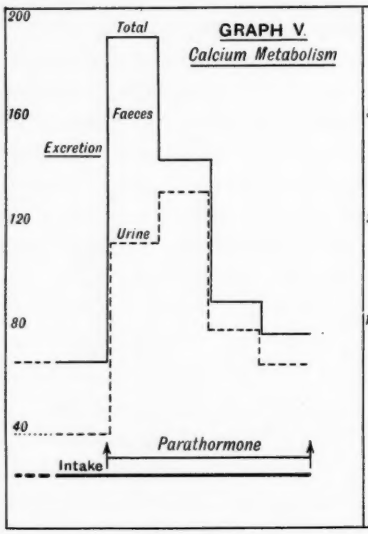

Fig. 391.

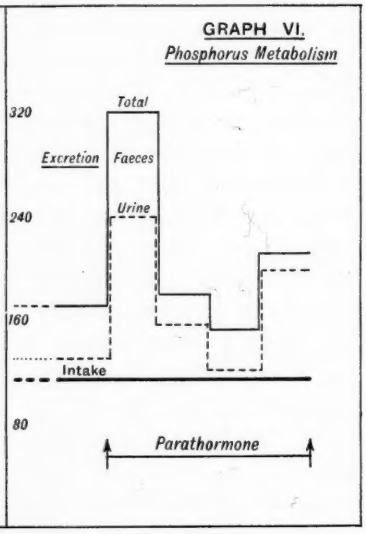

Fig. 392.

four periods on parathormone, the animals were killed. The serum calcium had returned to below the original figure, in spite of the dose of parathormone having reached by this time 160 units per day. (The last phosphorus estimation was unfortunately spoiled.) As regards the fæces, the metabolism work presented

some difficulty, because on this low calcium and practically non-residue diet the quantity of fæces was very small indeed and variable. The fæcal results in the metabolism graphs are therefore somewhat inaccurate, but as the urine excretions are exact, the curves are substantially correct. *Table VIII* shows the figures for the excretion of calcium and phosphorus in the urine and fæces in relation to the intake and serum values of these elements. *Figs.* 391, 392 are metabolism charts of calcium and phosphorus respectively, constructed from the data in the table.

The results show an extraordinary reaction to the parathormone. The first period before injection shows the continuous negative balance sustained by the rabbit as the result of lack of calcium in the diet, a loss of about 40 mgrm. a day. The response to the first dosage of parathormone was immediate, the negative calcium balance being increased to 188 mgrm. of calcium lost per day. In the second period, with double the dose of parathormone, the response was less, 143 mgrm. of calcium lost per day; in the third period the loss was 87 mgrm. and in the fourth 75 mgrm. per day. The response of the phosphorus metabolism was even more unusual; only in the first period on parathormone was there an extra excretion of phosphorus. Some compensating mechanism was therefore established against the action of the parathormone, which was sufficiently powerful to overcome the effect of the increasing dosage given. The serum calcium reflects this change, rising slightly after the first two periods, but falling again at the end of the experiment. Post-mortem examination of the rabbits showed no abnormality in the soft parts, including the parathyroid glands. The bones showed the results of the prolonged decalcification, and were very thin and light compared with a normal rabbit. On splitting the femur lengthwise, the cancellous part had fewer and more delicate trabeculæ than the control, but the cortical bone in the shaft, although thinner, was hard and compact. The ribs were very frail, but the cortex was a thin, well-defined layer. Nowhere was any abnormality discovered in the marrow.

Histological examination of the ribs removed during the experiment confirmed these post-mortem findings. The first specimen, taken before parathormone injection, showed the effect of calcium deprivation, but the thin cortical layer was composed of laminated bone with well-formed Haversian canals, while active hæmogenesis was proceeding in the normal marrow. The young animal, in fact, having been almost deprived of calcium from the age of eight weeks to four months, nevertheless made the best possible use of what it had, and laid down the normal structure of compact bone in the skeleton. The second rib resected showed very little difference from the first, the extra drain of 150 mgrm. of calcium daily for eight days having produced no apparent histological change, while microscopic examination of the ribs and femora obtained post mortem showed the same picture. No fibrosis was to be found anywhere in the marrow, no osteoclastic activity, and no new osteoid bone.

In view of the absence of bone effect, and the unaccountable compensation to the parathormone developed by these rabbits, a further experiment was arranged. Jaffe and Bodansky found that the effect of parathormone on the bones of their dogs was much more marked the younger the animal, the most pronounced effect being produced on very young puppies. Also they were able to obtain their effect on the bones irrespective of the amount of calcium in the diet, the only difference

being that the animals on a high calcium diet suffered more severely from the toxic symptoms of hypercalcæmia than did those protected by a low calcium diet. However, as I had so far failed to produce in rabbits anything more than a slight rise in serum calcium, it was decided this time to use very young animals and to give them an adequate diet in all respects, although controlled by the needs of the metabolism work.

Experiment 6.—Two young rabbits 6 weeks old, from the same litter, were kept in the metabolism cage on a constant daily diet of 150 grm. of cabbage and 75 grm. of oats, equivalent to a daily intake of 195 mgrm. of calcium and 322 mgrm. of phosphorus. The metabolism periods were reduced to three days, and a preliminary period of twelve days on this diet was allowed before the injections of parathormone were begun, in order that equilibrium between intake and excretion should be established. During these four periods the calcium and phosphorus balances, serum concentrations, and plasma phosphatase were determined, standard X-rays were taken, and a portion of rib was resected from each rabbit as before.

Table IX

3-Day Periods	Calcium					Phosphorus					Plasma Phosphatase Units per c.c.
	Serum	Intake	Excretions			Serum	Intake	Excretions			
			Total	Urine	Fæces			Total	Urine	Fæces	
1	–	535	624	360	264	–	1042	1034	26	1008	
2	–	322	434	283	151	–	738	680	16	664	
3	–	447	498	191	307	–	828	884	16	868	
Rib resected											
4	R_1 10·2 R_2 12·6	485	464	202	262	4·0 4·1	944	628	13	615	0·18 0·15
Injection of parathormone: 40 units daily											
5	–	422	**1282**	320	963	–	885	649	9	640	
6	R_1 **13·0** R_2 **13·6**	400	**943**	341	602	3·7 3·3	865	404	12	392	0·26 0·19
7	–	422	**775**	222	533	–	885	366	6	360	
8	R_1 11·1 R_2 12·4	422	**682**	153	529	3·6 3·6	885	400	8	392	
Rib resected											
9	–	407	**614**	163	451	–	817	495	17	478	
10	–	422	**714**	258	465	–	885	404	19	385	
11	R_1 10·6 R_2 12·8	422	**559**	141	418	3·9 4·7	885	494	4	490	0·23 –
12	–	404	616	272	344	–	865	350	7	343	
13	–	359	403	180	223	–	596	505	5	500	
Animals killed—ribs removed											

The investigation period then commenced, and the animals were given a constant dose of 40 units of parathormone daily by the intramuscular route. After twelve days, during which the serum changes were followed, another portion of rib was taken from each rabbit for histological examination. During this first part of the experiment, as in *Experiment* 5, the serum calcium of each animal was raised, and there was a marked immediate rise in the amount excreted. During the succeeding twelve days, the excretion of calcium declined progressively, and

the serum calcium returned to its previous level. After two further periods the animals were killed and the third specimen of ribs was obtained post mortem. *Table IX* is a record of the intake and serum values of calcium and phosphorus and the excretions of these in the urine and fæces respectively, together with estimations of the plasma phosphatase. *Fig.* 393 is a calcium metabolism chart of the experiment with the serum calcium changes of the two animals also shown.

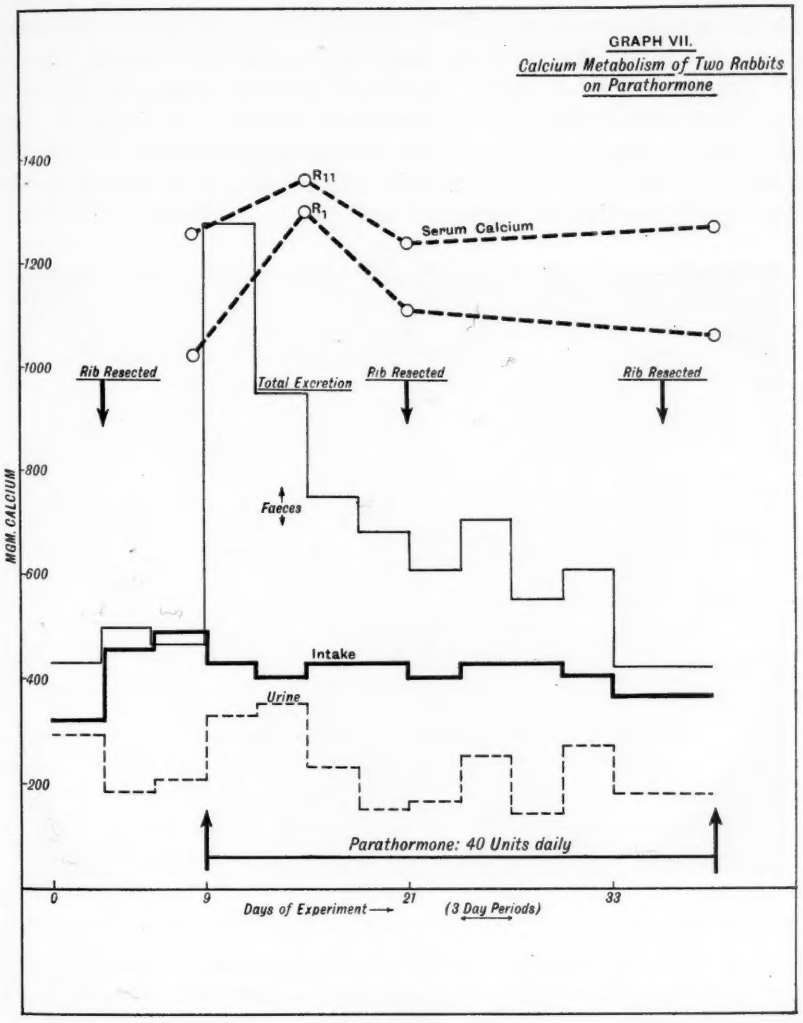

FIG. 393.

The biochemical results are very similar to those in the preceding experiment and emphasize the following points :—

1. There is an immediate response to the first injections of parathormone, by a marked increase in the excretion of calcium.

2. There is a corresponding rise of serum calcium in the early part of the injection period.

3. The increased excretion of calcium is more by way of the fæces than the urine (unlike human hyperparathyroidism : *see Case* 2, p. 586).

4. Following the initial excessive excretion, the calcium loss diminishes, *in spite of the continued administration of the parathormone*, until at the end of the twenty-four days the excretion is little more than the intake.

5. The phosphorus metabolism responded, if at all, by retention of phosphate rather than increased excretion. This may be associated with the fact mentioned earlier, that rabbits on this type of diet excrete practically no phosphate in the urine (*see Table IX*).

This remarkable result is reflected strikingly in the three specimens of rib. The first specimen (the control) was hard, broke like match-stick, and could be splintered but not cut by a knife. Section of this rib showed a normal compact laminated cortex, with normal red marrow in the centre.

Before the second resection the thorax was palpated and one or two rather plastic areas were felt at the anterior ends of the ribs, in particular in the stump of the rib already resected—at some distance, however, from the cut end.

FIG. 394.—Section of rib showing decalcification by parathormone (Exp. 6, First Phase).

This was not corroborated by the radiograms, but respiratory movements rather blurred the outlines of the anterior ends of the ribs. (Also no diminution of density of the shadow or alteration of bone pattern was observed in the long bones.) However, the plastic part of the same rib from which the first portion had been removed was selected for resection, and after removal it was found to be soft and elastic, and could be bent without breaking and cut with a knife. This rib was unfortunately left too long (though only eighteen hours) in the decalcifying fluid, and became somewhat broken up before it could be mounted in paraffin. The section, however, of which a microphotograph is reproduced (*Fig.* 394), shows striking decalcification of the cortex, only the distorted connective-tissue framework remaining. The marrow, moreover, shows multiple small hæmorrhages into

its substance, while the line of demarcation between cortex and marrow is irregular and indistinct as compared with Rib 1. It is to be noted particularly that in this rib, removed at the height of decalcification, there is no evidence of osteoclastic activity and no giant cells are present, except those of the hæmatogenic type in the marrow. The marrow hæmorrhages, however, are important in connection with the appearances in Rib 3.

The third specimen of rib was obtained post mortem. When the side of the dissected thorax was viewed by transmitted light, speckly areas were observed in one or two of the ribs, which, however, were not softened. Specimens were taken for section from the speckly areas and from the normal-looking parts. Sections of the latter showed fairly normal appearances, and nothing abnormal was present in the marrow; the cortex was sharply demarcated from the marrow, was well calcified, and contained no giant cells or fibrosis. Sections of the speckly parts of the rib showed striking changes (*Fig.* 395), the classical histological appearance

FIG. 395.—Section of rib (high magnification) during stage of repair of decalcification and marrow hæmorrhage. Note fibrosis of marrow and giant cells—typical osteoclasts (Exp. 6, Second Phase).

of osteitis fibrosa. The cortex was partly recalcified, not as a continuous layer of compact bone, but broken up into separate small areas by young fibrous tissue. The marrow was entirely replaced by fibroblasts of the same shape and type seen in sections of von Recklinghausen's disease, and numerous giant cells identical in appearance with those in clinical osteitis fibrosa were present. They were large, rounded cells, with from two to six nuclei in the centre. Some of them lay amongst the fibroblasts which had replaced the marrow, but most lay in apposition to areas of bone. The bone in contact with the giant cells was eaten away in the manner characteristic of osteoclasts, the giant cells lying in typical Howship's lacunæ. Moreover, examination under the high power of the microscope showed that the giant cells presented a different aspect according to their size. The large, fully formed cells, particularly the few lying alone in the young fibrous tissue, had a rounded, oval cytoplasm, with five or six circular nuclei in the middle of the cell.

The immature cells, characteristically those forming along an edge of bone, had fewer, more elongated nuclei, which corresponded to processes of cytoplasm radiating from the cell. The appearances were, in fact, that the giant cells were being formed by fusion of two or three of the proliferating connective-tissue cells round about. The stimulus to the fusion seemed to be the presence of an irregular edge of bone amongst the proliferating cells, and all stages from the early fusion to the fully-grown giant cell could be seen.

Other bones of the animals were examined post mortem, but none of these appearances was found. Only one abnormality was discovered—namely, an area of apposition of new bone on the endosteum of the shaft of one of the femora. The new bone had destroyed and replaced part of the marrow, remains of which could be distinguished in the new tissue.

The soft parts of the animals showed no abnormality; there was no evidence of metastatic calcification, and the parathyroid glands appeared normal both macroscopically and on section.

Summary of Results of Parathormone Experiments

1. Prolonged injection of parathormone into an adult rabbit has no effect on the bones.

2. Rabbits fed from the age of 6 weeks to 4 months on a diet inadequate in calcium have a negative calcium balance, and develop osteoporosis of the bones, which, however, are otherwise normal in structure.

3. Young rabbits given a severe course of treatment with parathormone respond at first by an increased excretion of calcium and a rise in serum calcium.

4. Following this initial response, in spite of continued injection of parathormone, the serum calcium and the excretion of calcium return to normal.

5. Young rabbits on a low calcium diet do not develop bone lesions other than decalcification as the result of parathormone injections, whereas

6. Young rabbits on a high calcium diet do develop local lesions in the bones, similar in histology to human osteitis fibrosa.

7. The lesions in the marrow caused by excess of parathormone are: (*a*) Hæmorrhages in the stage of active decalcification; and (*b*) Fibrosis with giant-cell formation in the stage of healing.

DISCUSSION

The experiments of *Part I* show conclusively that phosphatase given to a rabbit, either over a long period of time, or by high dosage over a shorter period, or by a single massive dose, has no effect whatsoever on the bones. It must be concluded, therefore, that the increased plasma phosphatase observed in decalcifying diseases is the result of the disease process and not the cause of it. Moreover, it has been demonstrated (*Experiment* 3) that phosphatase in the plasma is very rapidly removed from the circulation, a little by excretion, but mainly by destruction. In generalized disease of bone, therefore, with a continuous high plasma phosphatase, if the enzyme is being continually removed, it must also be constantly replaced. This can be explained on the following hypothesis: Bones undergoing prolonged decalcification, as in osteitis fibrosa, are acted upon in two ways. On the one hand is the influence of the decalcifying agent, and on the other the response

of the weakened bone, whereby the osteoblasts are stimulated to form new bone. This they do by an increased output of phosphatase, which, however, is constantly being swept away into the circulation, causing the high concentration of phosphatase observed in the plasma, where, as I have shown, it is destroyed.

The struggle of the bone-cells to compensate in this way the drain of calcium is well illustrated in the mixed histological appearances of a decalcifying bone. The effect of the decalcification is seen in the enlarged Haversian canals and the spaces round the vessels. The reaction of the bone is indicated by the excess of osteoid material and the areas of actual calcification in it, where the local activity of the osteoblasts has concentrated enough phosphatase to cause formation of new fibre bone. This explanation of the high plasma phosphatase is independent of the nature of the decalcifying agent, which is in accordance with the observation that the plasma phosphatase is high in all types of decalcifying diseases, whatever the cause.

This view of the rôle of the osteoblast to form phosphatase is in accordance with a great deal of evidence relating to ossification in other circumstances, both normal and experimental. Many workers, including Leriche and Policard,[18] Jones and Roberts,[19] and others, have observed decalcification in bone in the presence of hyperæmia. According to my view, this is not so much a case of decalcification as of hindrance of recalcification by excessive removal of phosphatase, as the result of hyperæmia. That strain be the stimulus to the formation of phosphatase by the osteoblasts is in agreement also with the view so long held and amply proven by surgeons, that bone is laid down along the lines of strain, resulting, for example, in the mechanically optimum pattern of the trabeculæ in cancellous bone and the hollow compact shafts of the long bones.

Again, the theory of ossification here put forward is not at variance with the idea that the osteoblast is formed by metaplasia of ordinary connective-tissue cells. It merely suggests that the metaplasia consists in the formation of phosphatase by these cells, so that they lay down bone. Huggins[20] has shown that other cells which form phosphatase (e.g., bladder mucosa cells), when transplanted into connective tissues, give rise to the formation of ectopic bone. Furthermore, it has been shown by the writer (an unpublished experiment) and others that ligation of the renal artery in a rabbit results in conversion of the kidney, which contains a large amount of phosphatase, into a mass of bone, not an amorphous calcification as occurs in other degenerated tissues. In addition, true ossification has been reported in abdominal scars,[21] also a site of excessive tissue strain, and the formation of bone was immediately preceded by the appearance of phosphatase in it. It has been observed, too, that the formation of bone in the mesenchyme in the middle of the growing limbs of the fœtus—the line of continuous strain—also coincides with the appearance of phosphatase in this situation.

The theory of ossification put forward, therefore, is that connective-tissue cells respond to strain of continuous type by the formation of phosphatase, whereby bone is laid down in the matrix round the cells, which thus become typical osteoblasts.

However, to return to the subject of the high plasma phosphatase, it must not be supposed that this should cause a general deposition of calcium. The calcifying power of the phosphatase in the osteoblast lies in the *local* concentration of its action, whereby the amount of phosphate ions around the cell is increased, and

calcium, which was in equilibrium in the general circulation, is precipitated. A diffuse increase in phosphatase would merely cause a permanent slight shift in the calcium-phosphorus ratio in the tissues, without any precipitation of solid salt.

With regard to parathormone, the absence of any effect on adult rabbits is comparable with a similar result by Bauer[22] and his colleagues on adult rats, and by Jaffe and Bodansky[23] on guinea-pigs, while even in dogs the latter workers had difficulty in producing an effect in adults, except with very large doses. But it has been shown that young rabbits do respond to the drug, although temporarily. Indeed, the most striking result of the experimental work is the compensation to the action of parathormone developed by young rabbits, and demonstrated by the changes in serum calcium, calcium excretion, and bone histology. Where, however, the bones have been already subjected to prolonged decalcification, as in *Experiment* 2, the extra drain of calcium due to the parathormone seems to be distributed evenly over the skeleton, and there are no areas of severe damage as in *Experiment* 3. This may be explained by the protection afforded by the low calcium diet (*see below*) or perhaps by the somewhat greater age of the rabbits in the former experiment.

Jaffe and Bodansky found that the effect of parathormone was more pronounced the younger the dog, an observation that is in agreement with mine, but they were able to produce a relatively permanent effect on the bones of puppies, with only a small fraction (2 to 5 units) of the parathormone given to my rabbits. Moreover, the effect was a continuous one, although it diminished in intensity as the dog grew older, whereas in rabbits the effect was very transient. It was, in fact, remarkable how rapidly the affected parts of the ribs became first decalcified and then recalcified (albeit with other changes) in the space of one month.

The nature of the compensatory process is not clear. Pugsley[24] reported a similar compensation in rats and was able to show that it was not due to an immune body in the serum, for inoculation of an untreated rat with serum from an 'immune' rat did not protect it from the parathormone.

It is possible that man also may have a mechanism of compensation to parathormone, although slight compared with the rabbit, as it has been noticed that the curative effect of parathormone in cases of tetany following parathyroidectomy diminishes steadily the longer it is used. Apart from the question of compensation, there is a metabolic difference between the human being and the rabbit in the response to parathormone, for, as these experiments show, the resulting increased excretion of calcium occurs by way of the fæces in the rabbit, whereas in man the excess is eliminated almost entirely by way of the urine (*Case* 2, p. 586). It has been shown that the rabbit excretes no phosphate in the urine on what is, for this animal, a normal diet (cabbage and oats), whether given parathormone or not. But Albright, Bauer, and Aub have shown that the decalcifying action of parathormone in ordinary doses in man is the result of excessive phosphate excretion in the urine. It seems probable, therefore, that the compensation which occurs in rabbits, but not human beings, is connected with this difference in phosphate metabolism in the two species.

However, in spite of the compensation, it is quite clear that parathormone will produce localized lesions of osteitis fibrosa in the ribs of rabbits. Moreover, it seems that the question of how the lesion developed can be answered by these experiments, particularly *Experiment* 6.

This experiment is distinctly divisible into two phases—decalcification and compensation. The decalcification in the first phase is the direct effect of the parathormone. It is localized in type, affecting especially the ribs at their sternal ends, and is accompanied by hæmorrhages into the marrow. The cause of the hæmorrhage is probably as follows: It has been shown that hypercalcæmia is toxic to body cells, and that in high doses parathormone causes a rapid degeneration of the viscera. Now the concentration of calcium in the blood of the capillary vessels at the actual site of decalcification, must be much greater than that in the general circulation. Consequently, these vessels are subject to the most toxic action of the calcium, with the result that the endothelium of the bone capillaries is damaged and extravasation of blood takes place into the marrow. The dependence of the hæmorrhage on hypercalcæmia in this way would also explain the absence of hæmorrhages in the rabbits on a low calcium diet, as those animals had a correspondingly lower serum calcium than those on an adequate calcium diet. In the latter animals the extra concentration of calcium in the bone capillaries, added to the general high serum calcium, was sufficient to cause the hæmorrhages into the marrow.

It seems, therefore, that marrow hæmorrhages depend on the severity of the decalcification, whereby calcium is concentrated in the vessels of the bone to such a degree as to damage the vascular endothelium.

To return to the second phase of my experiment, it was found that where there had been no damage to the marrow by hæmorrhage, the bone recalcified normally without alteration of structure, as in *Experiment* 5. Where, however, the marrow had been damaged by hæmorrhage it was replaced by a proliferation of connective-tissue cells, the hæmopoietic elements being removed by phagocytosis. It was at this stage, and not before, that the giant cells made their appearance. Moreover, the giant cells appeared to be formed *in situ* from the proliferating (phagocytic) cells, and were then indistinguishable from ordinary osteoclasts. Indeed, the formation of giant cells seemed to be stimulated by the presence of irregular bone. If it be accepted that these giant cells are essentially the same as ordinary osteoclasts, the absence of osteoclasts in the stage of decalcification is significant, for it indicates that osteoclasts take no part in decalcification by parathormone. The giant cells, however, appeared when there was real osteoclastic work to do in remoulding the damaged bone to the normal structure. The irregular bone laid down among the fibrous tissue was mechanically useless to the strength of the bone, and it was these islands of bone that the giant cells were absorbing. Here, then, is an apparent distinction between osteoclastic activity and the removal of calcium for metabolic purposes. In metabolic decalcification too slow to cause damage to the bone capillaries, the histological picture is one of simple solution of lime salts —halisteresis—with large spaces round the vessels, but no osteoclasts. If, however, phagocytic activity is aroused by marrow damage, in a disease like osteitis fibrosa with irregular deposition of bone, the local phagocytes fuse together to remove the unwanted fragments.

This conception of the giant cells as a part of the cellular reaction to the hæmorrhage is in accordance with the views of Kolodny,[25] Codman, and Mallory. The first quotes experiments by Konjetsny, who produced marrow hæmorrhages by mechanical traumata and found that they healed either by connective-tissue-cell proliferation, with giant cells of this type, or that small cysts were formed. Kolodny then supposes that, their phagocytic function complete, the giant cells remain

amongst the connective tissue and form the giant-celled tumours of von Recklinghausen's disease or disappear and leave cysts. This view of the disease is in accordance with many of its clinical characters—for example, the age of onset and the distribution of the lesions. The hæmorrhages would naturally occur when and where the bones are most vascular, and so the disease typically arises in young people, and, except in advanced cases, the cysts and tumours which follow the hæmorrhages are mainly at the ends of the bones. When it is also remembered that von Schupp[26] has reported cases of true hyperparathyroid decalcification without giant-cell tumours or cysts, it seems clear that these are due, not specifically to parathormone, but to any agent that will decalcify sufficiently rapidly to cause vascular damage in the bone and hæmorrhages into the marrow.

If one may review the position of von Recklinghausen's disease in the light of these findings, there are the following points to consider :—

1. The hypercalcæmia is definitely due to hyperparathyroidism, and to no other cause.

2. The low serum phosphorus is an effect of ionic dissociation, and is not specific to parathormone.

3. The high plasma phosphatase is indicative of the reaction of the osteoblasts to the decalcification, and is not specific.

4. The excessive excretion of calcium in the urine, although not specific to hyperparathyroidism (*see Case* 4, p. 588), is strongly suggestive of it.

5. The histological appearances—the extreme decalcification, marrow fibrosis, cysts, and giant-celled tumours—are indicative of a powerful decalcifying agent. Hyperparathyroidism is the most likely condition to produce them, although other causes are possible.

A typical case of hyperparathyroidism, therefore, presents all the above characters, which, taken together, establish the diagnosis, but only one of these is itself pathognomonic—the absolute hypercalcæmia.

SUMMARY OF CONCLUSIONS

1. The high plasma phosphatase in decalcifying disease is indicative of the extent of the bony reaction.

2. A suggestion is put forward with regard to the mechanism of the physiological process of ossification.

3. A distinction has been suggested between metabolic decalcification and the moulding of the bones by osteoclasts.

4. Differences in phosphate metabolism between rabbits and human beings have been indicated to account for—

5. The compensation established in rabbits to the effect of parathormone.

6. Areas of bone showing the classical histological features of osteitis fibrosa have been produced in rabbits by parathormone.

7. These features have been shown to be the result of the healing of marrow hæmorrhages and are not necessarily specific to the action of parathormone.

8. The giant cells have been shown to arise *in situ* by fusion of proliferating connective-tissue cells.

9. The giant cells so formed are indistinguishable from osteoclasts.

APPENDIX

During the course of this work, various clinical cases of abnormal calcium metabolism in the wards of St. Bartholomew's Hospital were investigated. A few of these are appended to illustrate some of the statements made in this paper. Attention was concentrated on the serum calcium and phosphorus, and plasma phosphatase, and their relation to the excretion of calcium. The technique of the calcium and phosphorus balance experiments was as follows :—

The patient was kept in bed on a fixed diet, low in calcium, but with a sufficient calorie value for the requirements of basal metabolism. The proportion of foodstuffs was adjusted to give a balance between acid- and alkali-forming foods in order to avoid the effects of acidosis. At the end of eight days of this diet, the intake and output of calcium and phosphorus had become steady, and the experimental period proper commenced and continued for a fortnight. The urine was collected in forty-eight-hour specimens, and the fæces in four-day specimens, marked off by doses of carmine by mouth. The excreta were measured, and aliquot parts analysed by the method described above in the work on rabbits.

The results of the analysis of four cases are here reproduced—cases of renal rickets, of typical hyperparathyroid osteitis fibrosa, before and after removal of a parathyroid adenoma, a case of non-parathyroid osteitis fibrosa, and one of early Paget's disease.

CASE REPORTS

Case 1.—**Renal rickets.**

The case of renal rickets referred to in the introduction was a typical one. It was a youth of 19 with advanced chronic parenchymatous nephritis, and a blood-urea of 80 mgrm. per 100 c.c., which later rose to nearly 400 mgrm. This boy had marked decalcification of all bones, but no deformities. The plasma contained 0·97 units of phosphatase per cubic centimetre, about ten times normal—indicative of a pronounced bony reaction.

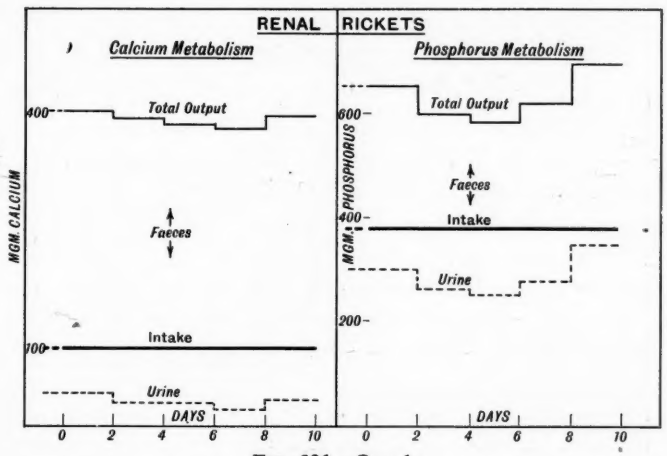

FIG. 396.—*Case* 1.

The serum phosphorus was high, 6·75 mgrm. per 100 c.c., and the serum calcium was correspondingly low, 8·8 mgrm. per 100 c.c. *Fig.* 396 illustrates the metabolism of calcium and phosphorus. There is a marked excretion of calcium, about four times the intake, and almost the whole of it is eliminated by the bowel and very little by the damaged kidneys. The excretion of phosphorus, also by the colon, is greater than the intake in spite

of the phosphate retention by the kidney. The mechanism of the whole process is: (1) Phosphate retention by the kidney; (2) Elevation of serum phosphorus, with depression of serum calcium; (3) Excretion of the excess phosphorus by the bowel as calcium phosphate; and (4) Mobilization of further calcium phosphate from the bones to make up the loss. In this way a continuous process of decalcification is established.

Case 2.—**Hyperparathyroidism.**

This was a typical case of hyperparathyroidism of long standing. The serum calcium was 14·7 mgrm. per 100 c.c. and the serum phosphorus was 1·47 mgrm. per 100 c.c., which illustrate the absolute hypercalcæmia and the consequent depression of the serum phosphate, in accordance with the law of ionic dissociation. Decalcification with giant-celled tumours

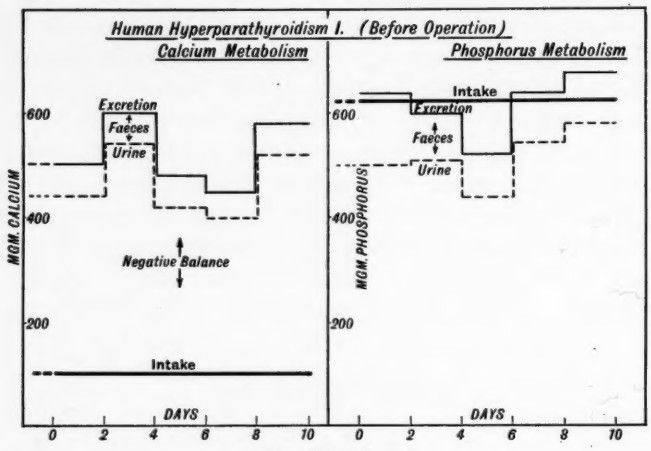

FIG. 397.—*Case* 2.

and cysts in the bones had been treated for years, and the patient had multiple deformities. The plasma phosphatase was raised to 0·33 units per cubic centimetre, only about four times normal, indicating that the resistance of the osteoblasts was at a low ebb. In the metabolism graphs (*Fig.* 397) it will be seen that there was a negative calcium balance of 350 mgrm. of

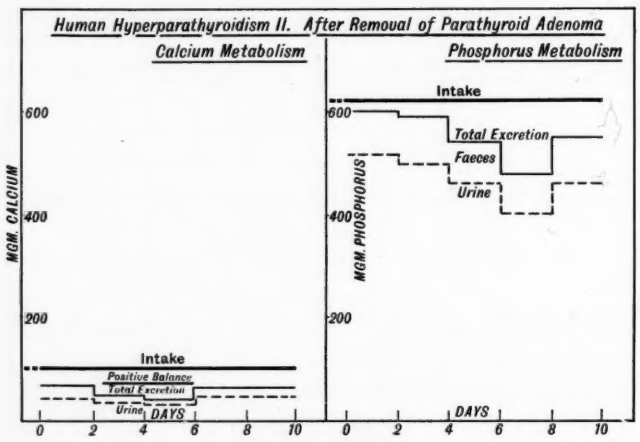

FIG. 398.—*Case* 2.

calcium per diem. The phosphate metabolism does not show any marked abnormality. The curves are characteristic of human hyperparathyroidism, in that the excretion of calcium and phosphorus is almost completely by way of the urine, differing in this respect from rabbits.

After operation the serum calcium fell immediately to 8·4 mgrm., and the serum phosphorus fell to 2 mgrm., rising during the next fortnight to 2·9 mgrm. At this time mild symptoms of tetany were observed, which, however, quickly disappeared. Five months after operation the patient's metabolism was again investigated on the same diet as previously. The serum calcium had risen to 11·2 mgrm. and the phosphorus to 4·4 mgrm. per 100 c.c., while the plasma phosphatase was 0·9 units per cubic centimetre—all figures

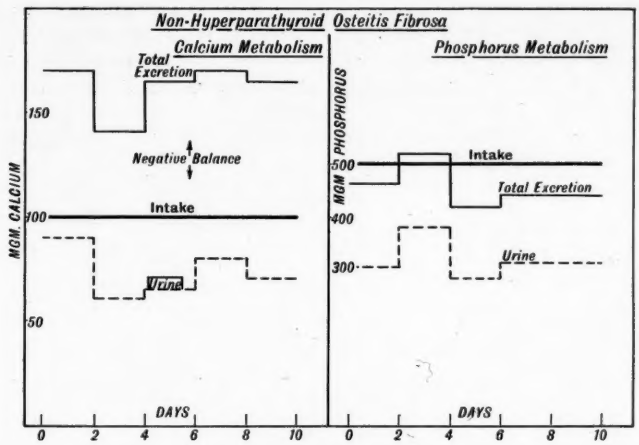

FIG. 399.—*Case* 3.

within normal limits. A striking change will be seen in the metabolism graphs (*Fig.* 398), the previously negative calcium balance having become a positive one of 40 mgrm. of calcium laid down each day in the bones. The phosphate metabolism charts are little altered.

Case 3.—**Non-parathyroid osteitis fibrosa.**

In contrast with the preceding case, this was one of non-parathyroid osteitis fibrosa, established by histological examination of the bones. Serum examination, however, showed

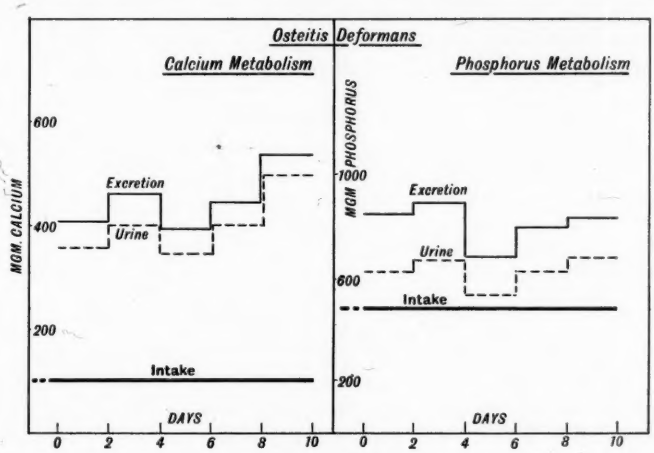

FIG. 400.—*Case* 4.

a low calcium, 8 mgrm. per 100 c.c., and phosphorus 2·6 mgrm. per 100 c.c., evidence of diminution of parathyroid activity rather than the reverse, perhaps in compensation for the other agent at work which was decalcifying the bones. The bony response was again not great, indicated by the plasma phosphatase of 0·21 units per cubic centimetre. The disease was of the multiple localized type, about half the bones of the body being affected. The

metabolism graphs (*Fig.* 399) indicate a slight negative calcium balance, the excretion, however, being rather more in the fæces than the urine, in contradistinction to the hyperparathyroid case. The cause of the decalcification in this case was not discovered.

Case 4.—**Early Paget's disease.**

The patient was a man of 49 admitted as the result of bilateral coxa vara, who had noticed symptoms for only eighteen months. There was diffuse decalcification of the femora, tibiæ, and humeri, but no bone cysts or tumours. The serum calcium was 11·5 mgrm. per 100 c.c. and the phosphorus 3·6 mgrm. per 100 c.c. The metabolism graphs (*Fig.* 400) show a striking resemblance to those of hyperparathyroidism, the marked negative balances of calcium and phosphorus occurring in each case by way of the urine. Such a graph is unusual in Paget's disease, but the disorder consists of a period of decalcification, of which this case is an example, followed by compensation and sclerosis of bone, with corresponding variations in the metabolism figures.

I should like to express my thanks to Professor Kettle, Dr. Harrison, Dr. Archer, and Miss K. Hare for valuable help with technical points in this work and for permission to use the facilities of the Pathological Department of St. Bartholomew's Hospital. I wish to thank also Professor Gask, Professor Fraser, Mr. R. C. Elmslie, and Mr. G. L. Keynes for their interest and for permission to investigate their cases, and Mr. Paterson Ross, to whom I looked for inspiration on this subject.

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ETIOLOGY OF TRAUMATIC SHOCK

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INTRODUCTION

The definition of traumatic shock has always caused difficulty to writers on the subject, and this difficulty has often been overcome by abandoning the attempt and providing instead a clinical picture of the syndrome. The type of traumatic shock with which this paper is solely concerned is frequent in civil practice. A very typical case was observed early in the course of the investigation. A 6-year-old boy was run over by a bus—the vehicle passed over both thighs—and he was admitted to hospital in a state of shock. In this state he died some twenty-four hours later. At autopsy there was much extravasation of blood into the muscles around the fractured ends of the femora, and this extravasation extended into the retroperitoneal tissues. There was intense pallor of the skin. The omentum, intestines, liver, and kidneys were also pale in colour, and on section of these organs the cut surfaces did not bleed. There was no evidence of congestion of the splanchnic vessels, nor were any petechial hæmorrhages observed. The lungs were pale and the heart was small, contracted, and only moderately full of blood. No vital organ had suffered injury, and the case was in every respect similar to one that prompted Crile, then still a student, to direct his energies towards a solution of the problem of shock. It must be remembered that whatever the ultimate explanation of shock, it was the application of this experimental work which enabled Crile to lay down the important principle of shielding the patient from all nociceptive impulses, whether physical or psychological. The same type of shock was produced experimentally in the cat in the classical experiments of Cannon and Bayliss, and their method has been used in the present series of experiments.

Much work has been done on the shock which may result from trauma to or even handling of the intestines and on the collapse which attends extensive burns of the skin, and efforts have been made to provide an explanation for shock which will also explain the fatal collapse of intestinal obstruction or general peritonitis. None of these conditions will be considered here, and any conclusions reached apply solely to traumatic shock of the type just described.

Although, as the literature amply shows, the syndrome of traumatic shock had always attracted the attention of English surgeons—the term was adopted almost in its literal form in France and in Germany—the problem assumed such proportions during the Great War that a new theory arose to explain the syndrome; it

might be truer to say that a very ancient theory was revived (*Lancet*, 1934, i, 1016). The importance of nervous impulses and of fluid loss into the traumatized area had always been recognized, but in the experiments carried out by Cannon it seemed to him that neither of these factors was adequate to account for the collapse and death which followed trauma inflicted on the thigh of the etherized cat. In 1910 Dale and Laidlaw had described the action of histamine on the experimental animal. Dale resumed this work with Richards and Laidlaw early in the war on account of the possible interest by analogy of the shock-like condition which large doses produced. Although the actual production of histamine from fresh animal tissues was only to be established beyond doubt by Best, Dale, Dudley, and Thorpe in 1926, Cannon was attracted by the possibility that this or some similar product was absorbed from the traumatized area, and some of his experiments lent support to this view. Although Dale, Laidlaw, and Richards were careful to point out the important respects in which the circulatory collapse of histamine poisoning differed from that following on trauma, there was a tendency for the toxic factor not merely to be granted a certain hypothetical importance but for it to be regarded as the main and most important agent in the production of the syndrome. To a large extent this tendency has persisted, at least in clinical practice, despite the volume of experimental evidence which has accumulated in the years following the war against the toxic theory of shock. Dale has recently pointed out that " many details of the work done in war have needed revision in the light of investigations made under the unhampered and unhurried conditions of more normal times."

The confusion which surrounds this problem sufficiently justifies a re-examination of the experimental issues as a preliminary to some new therapeutic measures which are under consideration. That a need exists for an improved treatment of traumatic shock requires little emphasis. McDowall, in a recent Arris and Gale Lecture, pointed out the benefits which should result from a more systematic study of the results of trauma. From the experimental side there is abundant proof of the inefficacy of intravenous infusions in the treatment of established shock. The work of Padgett and Orr disposes as effectively of one of the newer methods of infusion—the use of a solution of glucose combined with injection of insulin—as similar experiments, like those of Smith, disposed of the older type of infusion consisting of gum saline or normal saline. The case against the treatment of traumatic shock by intravenous infusions and the evidence against the toxic theory of shock were summarized by one of us (L. O'S.) in 1931, and from our clinical observation we would endorse the opinion recently expressed by Blalock that there is at present no satisfactory treatment for shock which has persisted for several hours. It has been our experience that the subject of severe trauma who does not show some signs of recovery under established modes of treatment within two or three hours of his injury is almost inevitably doomed.

It seemed clear that a therapy directed towards three possible factors—the existence of one, the toxic factor, being at any rate doubtful—was less likely to be effective than a therapy directed against two certain factors. As a corollary to this an attempt to assess the relative value of the two remaining factors has also been made. Although a final judgement has not yet been reached, enough evidence has accumulated to show that the fluid-loss factor does not occupy the position of almost exclusive importance which has been assigned to it by some recent workers.

Feldberg and Schilf have recently stated that none of the animal experiments so far published have sufficed to establish the truth of the toxic theory of shock. We would go further and state that, so far as the type of traumatic shock here considered is concerned, the animal experiments published, the experiments recorded in this paper, and such observations as have been made on the blood of traumatized patients quite definitely disprove the theory.

Two sets of experiments are quoted by Feldberg and Schilf as providing suggestive, although not final, evidence in favour of the toxic theory. The first consists of the experiments of Voegetlin and Dyer, who noted that rats—notoriously resistant to histamine (M.L.D. 900 mgrm. per kilo)—were also resistant to trauma. Ten rats were subjected to trauma and all recovered. There are no records of blood-pressure during and after trauma. It is difficult to assess the degree of trauma inflicted, for only by careful post-mortem examination and weighing of a traumatized extremity can the degree of trauma inflicted during life be ascertained. Once histamine as a cause of traumatic shock following trauma to the thigh can be excluded, the special idiosyncrasy of the rat towards histamine bears no more relation to the problem than do any other of his idiosyncrasies, of which there are doubtless many. The second experiments quoted are those of McIver and Haggard, who constructed an ingenious animal preparation by means of which the amputated lower extremities of one cat were supplied with blood from a second cat through an artificial vascular anastomosis. Trauma to the amputated extremities was followed by a fall in blood-pressure of the donor cat. Since it was quite impossible for nervous impulses to reach this animal, it was assumed that the fall in pressure could only be due to the passage of some toxic substance from the traumatized area. Again there is no record of the post-mortem appearances or weight of the traumatized limb, so that the factor of local fluid loss into the traumatized area is not controlled. We repeated one experiment of this type, and the fluid loss, although smaller than is usual following our method of trauma, seemed adequate to account for the fall in pressure obtained, because the setting up of the preparation involved a certain amount of incidental trauma and blood loss. We have also found it possible by means of a less elaborate preparation to isolate the lower limb from the general circulation and to establish the fact that, even when the venous ligatures carried out are adequate to prevent the absorption of histamine injected into the limb, trauma—provided the arterial supply is intact—leads to a typical onset of shock.

A complete résumé of the evidence against the toxic theory of shock which has been published in America and most European countries during the last ten years will not be attempted. The contributions of such experienced surgeons as Rehn and Coenen may be mentioned as having had an important influence on European opinion in this respect. A rather rare international agreement on a controversial issue is illustrated by a short list of workers who, for one reason or another, have decided against the toxic theory of shock—Parsons and Phemister (America), Bolten (Holland), Kalalova (Czechoslovakia), Ewig and Klotz (Germany), Simonart (Belgium)—and further search could enlarge this list almost indefinitely.

The publications which have a direct bearing on the work presented here are those of Blalock and his associates, of Parsons and Phemister, of Freedlander and Lenhart, of Schneider, Simonart, and Smith.

To Blalock we are indebted for the discovery of a satisfactory technique for

weighing the traumatized extremity. In the earlier experiments amputation was done through the thigh, and the negligible difference in weight between the normal and the traumatized extremity led Cannon to believe that the factor of local hæmorrhage could not be of importance. Blalock observed that the hæmorrhage and exudation of fluid which results after severe trauma to the thigh extends upwards into the muscles of the flank (we also observed this phenomenon in a fatal case of trauma of the thigh in man), and he found that if hindquarter amputation was carried out, a very significant difference in weight between the normal and the traumatized side could be demonstrated. Blalock also found that shock still developed when a limb was traumatized after a tourniquet had been applied so as to obstruct all vascular channels with the exception of the femoral artery. There was no path for absorption of any toxin, and Blalock attributed the shock to hæmorrhage into the traumatized area. Trauma to an extremity after occlusion of both arteries and veins was not followed by the development of shock, and this Blalock explained by the fact that under these conditions hæmorrhage into the traumatized area was impossible. Blalock also demonstrated that the infusion of blood from a shocked animal into a normal dog produced a rise in blood-pressure—not a fall as would be expected if a depressor substance were present in the circulation of the shocked animal. Thus Blalock failed to confirm the view of Cannon and Bayliss as to the toxic origin of traumatic shock, but he is prepared to accept the other main conclusion of these workers on the relatively unimportant part played by the nervous system. He himself has not published any observations on the effect of nerve section on the onset of traumatic shock, but he states that trauma carried out after a spinal anæsthetic still produces characteristic effects: details of these experiments have not been published.

Parsons and Phemister used seventy dogs in their series of experiments, and in most cases traumatized one thigh in the manner of Cannon and Bayliss. They were able to show that the blood from a traumatized extremity when injected into a normal animal failed to lower the blood-pressure. Another significant finding was that traumatized muscle from an animal which had developed shock, when removed from the body and treated by biochemical methods, gave as high a yield of vasodilator substances as did an equivalent weight of normal muscle. Clearly, if the shocked state had been even in part due to absorption of vasodilator substances from the traumatized area, a lower yield should have been obtained. It was found that a dog whose blood-pressure had been reduced to 60 mm. of Hg by the injection of histamine was remarkably resistant to hæmorrhage. In order to produce death in such an animal some 600 c.c. of blood had to be removed, while in a dog of similar weight but with a low blood-pressure following trauma 100 to 200 c.c. of blood constituted a fatal hæmorrhage. Shock due to a local production of some vasodepressor substances in the traumatized area should be averted by ligature of the main veins draining the area, but Parsons and Phemister found that this intervention hastened rather than retarded the onset of shock after trauma to an extremity. It is stated that concentration of the blood is a constant feature in histamine intoxication, but in none of their experiments was any change other than dilution of the blood observed. Parsons and Phemister also recorded that the blood recovered from the traumatized area showed no tendency to clot even if kept for some days. No explanation was found for this fact, although attempts were made to re ate it to an increased production of heparin as a response

to the trauma. This finding may possibly explain the comparative rarity of a blood-clot forming in the carotid cannula in our traumatized animals and the extreme frequency of such a complication in our histaminized animals.

Freedlander and Lenhart carried out experiments on trauma to the hinder extremity of the cat. They too found that concentration of the blood was not a feature of this type of experimental shock, although marked concentration occurred in the early stages of ether anæsthesia. They confirmed the view of Blalock that the important factor in traumatic shock was the local loss of fluid into the traumatized area. They conclude that the nervous factor is unimportant, and certainly some of the animals subjected to a preliminary section of the spinal cord died very soon after the infliction of trauma. At the same time it is significant that one animal which had been subjected to section of the spinal cord and excision of the lumbar sympathetic chain some days prior to trauma still maintained a blood-pressure of 118 mm. of Hg (initial level was 120 mm. of Hg) when the experiment was terminated some two hours later. At this period after trauma all the control animals were either dead or in a state of shock.

Simonart carried out some experiments on the cat in which the hind leg was subjected to trauma in the usual way. He concluded that there was no evidence for a toxic factor in the production of traumatic shock. In contradistinction to most other recent workers, Simonart considers that the nervous system plays a decisive rôle. He has carefully examined the original tracing on which Cannon based his view as to the relative unimportance of the nervous system under the conditions of experimental trauma (*Traumatic Shock*, p. 146). The tracing shows the blood-pressure of a cat subjected to trauma after section of the femoral and sciatic nerves. Simonart points out that 1 hour 40 minutes after trauma the blood-pressure was still 88 mm. of Hg, while in the control experiments a much lower level had always been reached in a similar space of time. Simonart records an experiment in which he subjected the limb to trauma after section of the femoral and sciatic nerves and occlusion of the femoral artery and vein. There was no significant fall in blood-pressure on releasing the vessels, while a similar intervention on a limb with an intact innervation led to a progressive fall in blood-pressure. In his opinion an intact nerve-supply is essential for the production of traumatic shock.

In 1928 M. I. Smith published a careful series of animal experiments on the subject of traumatic shock. He found that the blood removed from the femoral vein of a traumatized extremity when infused into a normal animal failed to produce a vasodilator effect. On the basis of this and some other experiments he decides that, whatever the mechanism of traumatic shock, local toxin production plays no part in the syndrome. While recognizing the importance of local fluid loss, Smith comes to the final conclusion that a depression of the peripheral vasomotor mechanism is the essential feature in traumatic shock—a return to the Meltzer inhibition theory of some thirty years ago.

Holt and Macdonald have recently repeated and confirmed some of the experiments of Blalock and of Smith. One point in their technique is at variance with our own findings. Ligature of the iliac vein—at least in the cat—does not prevent the absorption of histamine injected into the limb. A very complex series of ligatures is required in order to separate the vascular system of the lower limb from the general circulation, as will be demonstrated in the experimental part of this

paper. These workers accept the original experiments of Cannon and the later experiments of Freedlander and Lenhart as sufficient evidence against the importance of the nervous factor. They found in their own experiments that spinal anæsthesia failed to prevent *initial* fall in blood-pressure on traumatizing an extremity—there is no note as to the course run by these animals as compared with a normal control series. In short, while prepared to abandon the toxic factor in shock together with Blalock, they also follow him in his view as to the relative unimportance of the nervous factor.

Despite the frequent reference to the toxæmia present in cases of shock in man, it has been impossible to discover records of any experiment in which the administration of blood from such a patient to an animal has produced vasodilator effects. It is perhaps significant that when such experiments were carried out by Schneider using the blood of twenty patients, some of whom had suffered extensive burns and others operative trauma, in no case was the presence of a vasodepressor substance demonstrated.

One assumption in the hypothesis that attributes the symptom-complex of traumatic shock to the elaboration of vasodilator toxins in the area of trauma is that the amount of these depressor substances obtainable from the traumatized area must clearly be adequate in quantity to produce shock. The quantity of depressor substances which can be extracted from the tissue to be subjected to trauma must be of a quantitative order at least equal to the minimum dose necessary to produce the phenomena of shock.

Histamine and other vasodilator substances are readily extracted from most tissues. Lung and liver and some other tissues have a high content of these toxins, especially histamine. The amount prepared from muscle is very low even by the most careful biochemical extraction; Thorpe showed that extracts of voluntary muscle of the cat have a depressor activity equivalent to 1 mgrm. of histamine per kilo. of fresh tissue. The weight of the entire musculature of the thigh, only a small proportion of which is actually lacerated in our experiments, constitutes about 5 per cent of the total weight of the animal. Dale and Laidlaw have shown that while small doses of histamine, 0·01 to 0·1 mgrm., produced transitory and evanescent effects on blood-pressure, a dose of 1 to 2 mgrm. per kilo. of body weight, injected intravenously, will produce a typical shock-like failure of the circulation. Thus the dose of histamine necessary to produce shock in a 4-kilo. cat by the intravenous route is 4 to 8 mgrm. The total amount of depressor substances that can be obtained by thorough trituration and careful extraction from the 200 mgrm. of thigh muscle is only of the order equivalent to 0·2 mgrm. of histamine. These extracts, prepared biochemically in the laboratory from the entire muscle mass of the thigh, are in no way comparable to the much smaller amount of laceration of the thigh muscles as seen in the trauma adopted in these experiments. Dale has also shown that relatively large amounts of histamine can be tolerated by the cat when administered by slow intravenous infusion. In a series of experiments we have been able to demonstrate that the amount of histamine necessary to produce shock by intramuscular injection is ten times the amount necessary by the intravenous route (*Fig.* 401). In our experiments the hypothetical depressor substances produced as a result of trauma are presumably elaborated in the muscles. We may also presume that they are absorbed slowly into the circulation. Thus it becomes sufficiently clear that the total amount of toxins which could possibly be

freed for absorption, under the most favourable conditions, from the entire musculature of the thigh would prove inadequate to produce shock. Weiss, Robb, and Ellis have demonstrated that as much as 20 mgrm. of histamine per hour may be infused into the venous system of a man *without* producing any depressor effect on blood-pressure. Probably this represents the utmost amount of depressor substances

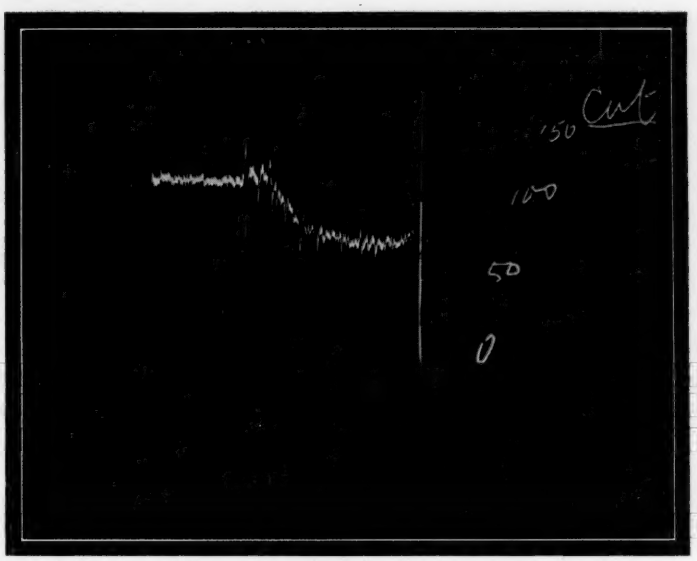


FIG. 401.—Intramuscular injection of histamine. *Cat* 87. 2500 grm. Chloralose. Tracheotomy. Initial blood-pressure 120 mm. Hg. Signals 1, 2, 3, 4, 5: 10 mgrm. histamine intramuscularly right thigh. Blood-pressure 75 mm. Hg. Time signal 30 seconds.

which can be obtained from the complete destruction and intensive extraction of more than 8 kilo of muscle. The difficulty, therefore, of assigning to the damaged muscle the rôle of producing an amount of toxins adequate to produce a lasting fall of pressure cannot be dismissed too lightly.

THE EXPERIMENTS

One hundred cats were used as the subjects of experiments. The animals were anæsthetized by chloralose (0·08 grm. per kilo) given intravenously in 10 c.c. of water. The blood-pressure was recorded by a carotid cannula and a mercury manometer. Trauma was inflicted by twenty blows of a heavy iron bar on one thigh. The skin remained intact, but in each instance the femur was broken, and at autopsy considerable injury to the muscles of the thigh could be demonstrated. No animal was allowed to recover from the anæsthetic, and in all cases a post-mortem examination of the abdominal and thoracic viscera was carried out. In estimating the increase in weight of the traumatized extremity, the lower half of the cat was amputated by a circular incision passing through the lower lumbar vertebræ, and the portion so removed was bisected by section of the symphysis pubis and the sacrum.

Our object was to reproduce experimentally the conditions found in the fatal cases that we had observed in practice. The milder degree of trauma which has

been used by some other experimentalists, achieved by repeated blows so graduated as to crush the muscles of the thigh but not to break the femur, produces a condition of the limb which has no doubt its physiological interest, but a condition which has rarely, if ever, its counterpart in surgical practice and certainly fails to conform to the type case on which this research is based.

SECTION I.—THE AREA OF TRAUMA AS A SOURCE OF TOXINS

Cannon and Bayliss demonstrated that the fall in blood-pressure which develops within about twenty minutes after local trauma to the thigh in anæsthetized cats fails to develop if, prior to trauma, ligatures are applied to the iliac artery and vein. In the only experiment recorded, the ligatures were removed after thirty-three minutes. The restoration of the blood-flow was attended by an immediate fall of pressure. They explained this phenomenon by the inability of a hypothetical depressor toxin to get into the general systemic circulation before the ligatures were removed. Our own experiments bearing on the supposed liberation of toxic substances are summarized under four headings, as follows.

1. **Occlusion of Venous Return.**—Parsons and Phemister found that trauma to an extremity, the femoral vein of which has been ligated, results in more rapid fall in blood-pressure and swelling of the limb than when the venous return is not obstructed. This is adduced as evidence against the theory that shock was caused

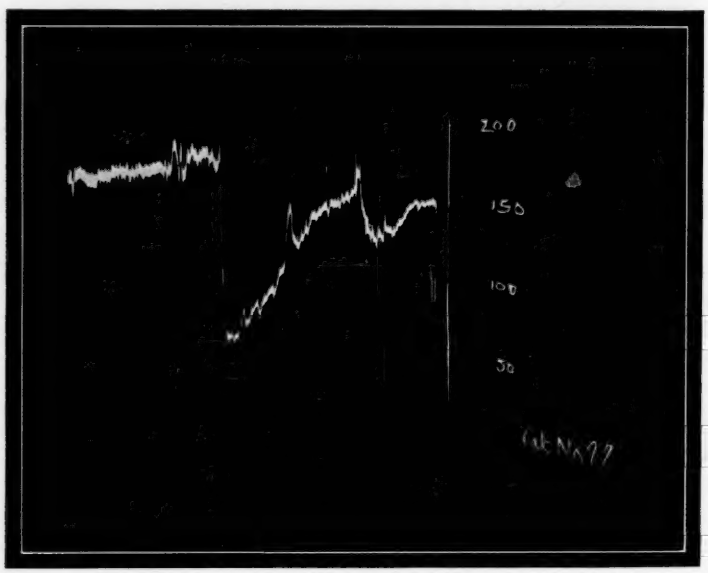


FIG. 402.—Ligation of common iliac vein and injection of histamine. *Cat* 97. 2500 grm. Chloralose. Tracheotomy. Initial blood-pressure 170 mm. Hg. Signal 1–2: Ligatures on right common iliac vein and section of vessel. Signal 3: 1 mgrm. histamine injected into tributary of right femoral vein. Blood-pressure falls to 75 and recovers. Time signal 30 seconds.

by a circulating toxin. Holt and Macdonald used ligature of the common iliac vein to prevent the passage of blood from the traumatized tissues into the circulation. But the following experiment shows that ligature of either the femoral or the common iliac vein is insufficient to prevent completely the venous return from the limb.

The right common iliac vein was exposed and divided between ligatures. Histamine injected into a tributary of the right femoral vein or into the thigh muscles produced a characteristic fall in blood-pressure (*Fig.* 402). Also, air introduced into the femoral vein post mortem passed readily into the vena cava by several anastomotic paths. Effective occlusion of the venous return was however attained by ligature of the femoral vein and its tributaries in the groin and the external, internal, and common iliac veins, and the inferior vena cava and its transverse iliolumbar tributary. After this procedure, injection of histamine into the thigh failed to affect the systemic blood-pressure. In a series of experiments, trauma applied to a limb with venous ligatures as above detailed evoked a rapid decline of blood-pressure and the appearance of a state of severe shock with an early fatal termination. In some experiments a tourniquet was applied tightly to one limb, only the femoral artery being excluded. Trauma to the thigh distal to the tourniquet produced a marked degree of shock and early death.

2. **Perfusion of the Area of Trauma.**—The searching analysis of the action of histamine and the detailed investigation of the production of histamine by Dale and his collaborators provided a basis for the theory that wound shock was caused by absorption of toxic products from damaged muscles. M. I. Smith has shown that blood removed from the clamped femoral vein of a traumatized limb and re-injected into the animal caused a rise and not a fall of blood-pressure. This observation was controlled by injecting a histamine solution peripherally into the clamped femoral artery and demonstrating a depressor response on injecting blood removed from the femoral vein of that side into the opposite femoral vein. Smith also found that a direct transfusion from the femoral vein of a traumatized limb into a second animal was not associated with any depressor effect on the blood-pressure of the recipient.

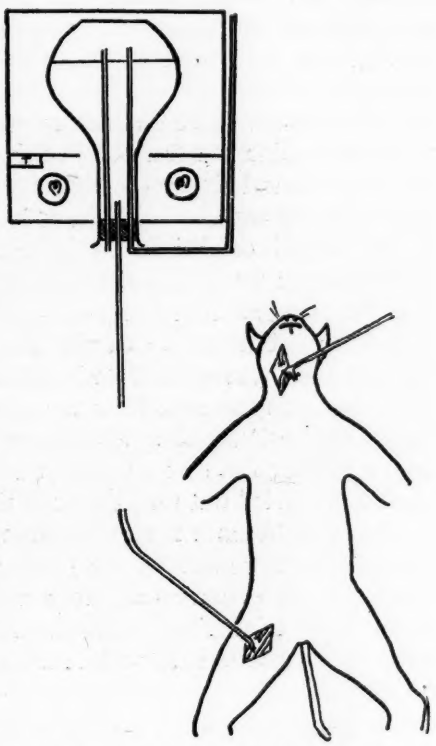


FIG. 403.—Perfusion of limb experiment.

We have performed a series of experiments on perfusion of a traumatized limb and failed to elicit any evidence of the presence in the traumatized tissues of vasodilator substances to which might be attributed the general vascular collapse of shock.

Perfusion of the limb was carried out in the following manner. An incision was made over the femoral artery in the groin. The vessel was dissected and ligatured. A cannula inserted into the peripheral segment of the femoral artery connected with a reservoir from which physiological saline at a constant rate and at body temperature could be supplied. This was secured by having an inverted flask of saline in a box, the temperature of which was kept constant by two filament lamps and a simple thermostatic device so

adjusted that the temperature of the saline at the cannula was kept accurately at body temperature. The arrangement of the apparatus for these experiments is shown in *Fig.* 403. The limb was then traumatized and, at definite periods after trauma, saline was allowed to flow into the femoral artery. A rise of blood-pressure was evoked, so that there was no evidence that any depressor principle was being carried into the circulation by the saline perfusing through the traumatized tissues. Saline infusion through the area of trauma was carried out immediately after trauma or at varying later periods; in some experiments a period of four hours elapsed. A possible criticism is that the *pressor* effect of the volume of the saline infusion neutralized the *depressor* effect of any vasodilator substances present. Histamine was therefore introduced into the traumatized area and on repeating the infusion, the rate of which was kept constant throughout the experiment, an immediate fall of pressure was produced (*Fig.* 404).

As a further control a solution of histamine equivalent to 2 mgrm. of the base was introduced into the thigh muscles of a cat after ligature of the external iliac artery. Thirty minutes later a cannula was inserted into the artery distal to the ligature and saline infused into the animal. A typical histamine response was produced, an immediate sharp drop of pressure with a slow recovery (*Fig.* 405). In *Fig.* 406 is illustrated the production of histamine shock by perfusion after 48 mgrm. of histamine had been injected into the traumatized thigh. Perfusion of the traumatized thigh for the same period of time previous to the introduction of the histamine had resulted in a rise in blood-pressure. The site of production of the hypothetical depressor toxins postulated in the toxæmic theory of shock is located in the muscles. Hence it is probably a more strictly accurate reproduction of the actual conditions to introduce the histamine solution into the muscles themselves as we have done in some of these experiments than to inject the drug into the clamped artery as practised by M. I. Smith and by Holt and Macdonald. In one experiment the external iliac artery was tied and the vein clamped. The leg was then traumatized and histamine injected into the area of trauma. When the clamp was removed from the vein and saline was perfused through the femoral artery, the resulting drop of pressure was no greater than that which resulted when an equivalent dose of histamine was injected into an untraumatized thigh and perfusion carried out under exactly the same conditions.

3. **The Search for Diffusible Products in the Systemic Circulation.**—Investigations undertaken to demonstrate depressor substances in the blood of shocked animals have been uniformly unsuccessful. Schneider prepared extracts of the blood of shocked patients and tested these for depressor activity with negative results. Normal serum he found contained a principle which induced contractions of the isolated intestinal muscle preparation of the guinea-pig. This principle, which has no depressor quality, is increased in cases of trauma and extensive burns. Small quantities of histamine added to the blood were recoverable by his method of extraction. Hence the blood of shocked patients contained no histamine-like substance. Other investigators failed to find any evidence of a toxin on injecting blood of shocked animals into normal animals. It was pointed out in the introduction that the experiments of McIver and Haggard are susceptible of a different interpretation from that which they postulated. The fall of pressure in an animal, the femoral vessels of which are utilized to supply blood to the amputated lower

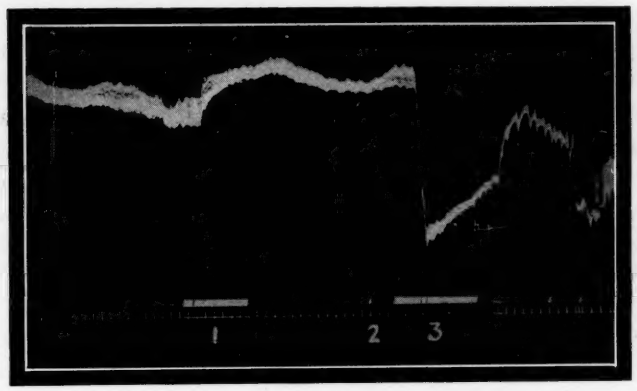


FIG. 404.—*Cat* 2. Saline perfusion of traumatized limb. Trauma to thigh—vessels clipped. Signal 1: Perfusion of traumatized limb 30 minutes later. Signal 2: 2 mgrm. histamine into traumatized area. Signal 3: Perfusion of traumatized limb. Time signal 30 seconds.

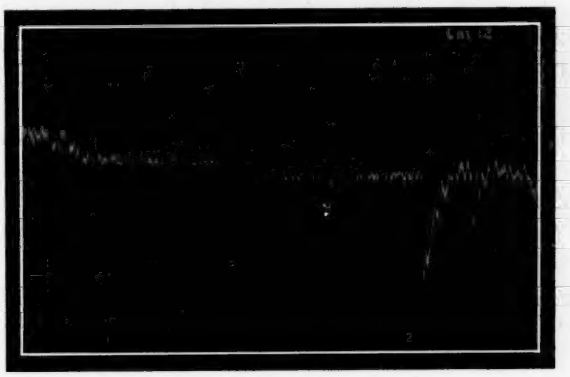


FIG. 405.—Perfusion of limb thirty minutes after injection of histamine. *Cat* 12. 3250 grm. Chloralose. Tracheotomy. Signal 1: External iliac vessels clipped. Two mgrm. of histamine into thigh muscles (L). Signal 2: Perfusion of limb (L). Time signal 30 seconds.

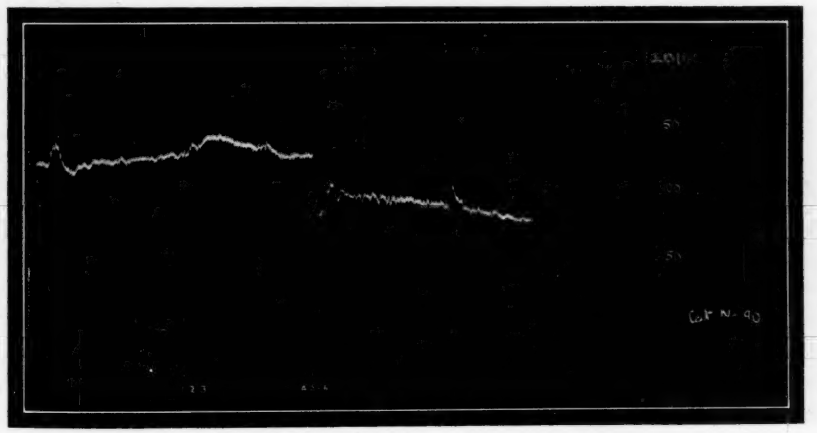


FIG. 406.—Perfusion of traumatized limb—injection of histamine—perfusion of limb. *Cat* 90. 4750 grm. Ligation of aorta, iliolumbar, middle sacral and common iliac arteries and femoral artery and its branches in the groin. Clip on external iliac vein. Signal 1: One hour after trauma— clips off external iliac vein. Signals 2–3: Perfusion with 40 c.c. saline for 160 seconds. Signal 4: 48 mgrm. histamine into traumatized area. Signals 5–6: Perfusion with 40 c.c. saline for 160 seconds. Time signal 30 seconds.

extremity of a second cat, on trauma to that extremity is as readily attributable to hæmorrhage into the traumatized tissues as to the absorption of a toxin.

Cross-circulation experiments are open to the criticism that the entire preparation tends to act as one unit. Fall of blood-pressure in one animal, whatever be its cause, results in bleeding from the second animal into the first until the pressures reach an approximate equilibrium. To obviate this difficulty we adopted a method based on vividialysis. The apparatus designed for this purpose is shown diagrammatically in *Fig.* 407. It consists essentially of two glass tubes (A and B), 15 cm. long, of 10 mm. cross-section, fitted at each end with rubber stoppers. The two limbs are connected together at one end by a short transverse tube, and each is furnished close to the opposite end with a short tube at right angles (D and E). Contained within each limb of this outer circuit is a tube of collodion membrane 8 mm. in diameter (P and Q), each securely ligatured at its end to the short glass tubes (R, S, T, and U) passing through the rubber stoppers. T and U are connected together by a short piece of rubber tubing. R and S serve as inlet and outlet for the inner circuit. There are thus two distinct U-shaped circuits within the apparatus. Cannulæ in the vessels of one animal are connected to R and S and of the other animal to D and E. The circuit of the blood of the one animal is distinct from that of the other except in so far as diffusion occurs across the collodion membranes. If one animal is traumatized, the presence of any depressor toxic product in its general circulation should presumably be recognized by a fall of blood-pressure in the second animal. The toxin would pass across the membrane from the circulation of the shocked animal to that of the other.

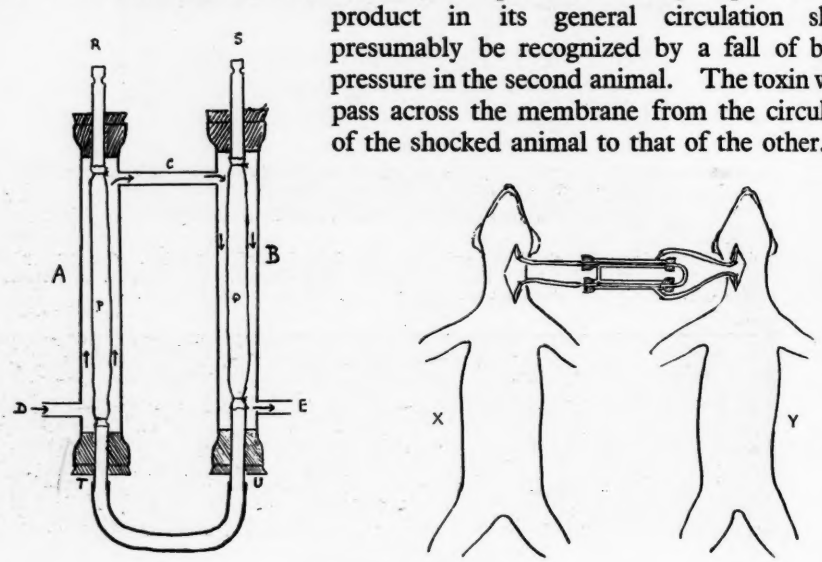


FIG. 407.—Vividialysis.

For each experiment with this apparatus two dogs were used. Novirudin was administered as an anticoagulant. The carotid artery on one side was exposed and dissected in the neck of animal X. Clamps were applied to its upper and lower ends. The artery was then divided and two cannulæ were inserted, one directed proximally, the other distally. The inner circuit of the apparatus (within the collodion membranes) was filled with physiological saline and the cannulæ connected by paraffined tubing to the inlet and outlet tubes (R and S in *Fig.* 407). The clamps were then removed. The integrity of the membranes and the free

flow of blood within them was verified. In a similar manner the second animal (Y) was connected to the outer circuit (limbs D and E). The fact that the blood was flowing freely could be established at any stage of the experiment by observing the pulsations in the outlet limbs or by feeling the pulse in the peripheral segment of the carotid. The blood-pressure of each animal was recorded from the femoral artery.

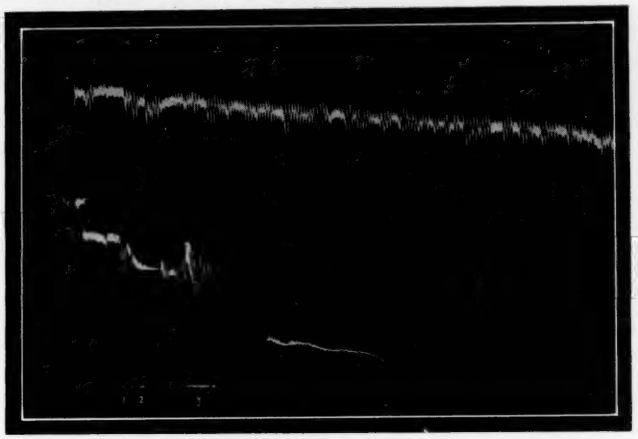


FIG. 408.—*Dogs* 1, 2. Vividialysis: Trauma. Each dog weighed 1500 grm. and the anæsthetic was morphia and nembutal. The two animals were connected to the dialyser and the circuits opened at Signals 1 and 2. *Dog* 1, lower curve; *Dog* 2, upper curve. Signal 3: Trauma to *Dog* 1. The traumatized dog went into shock and died thirty minutes later, while the blood-pressure of *Dog* 2 remained unaffected. Time signal 30 seconds.

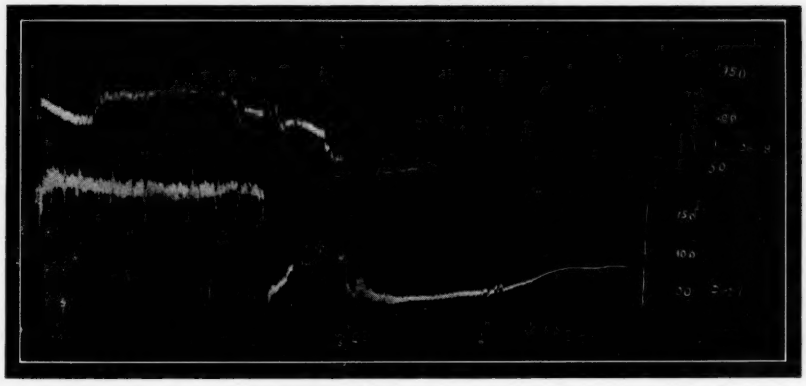
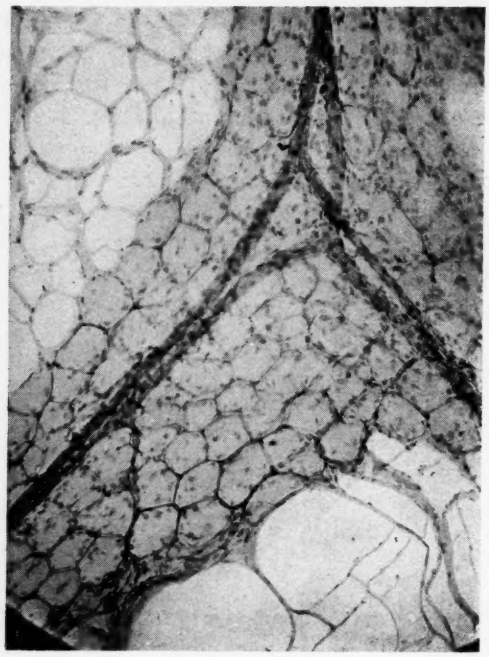


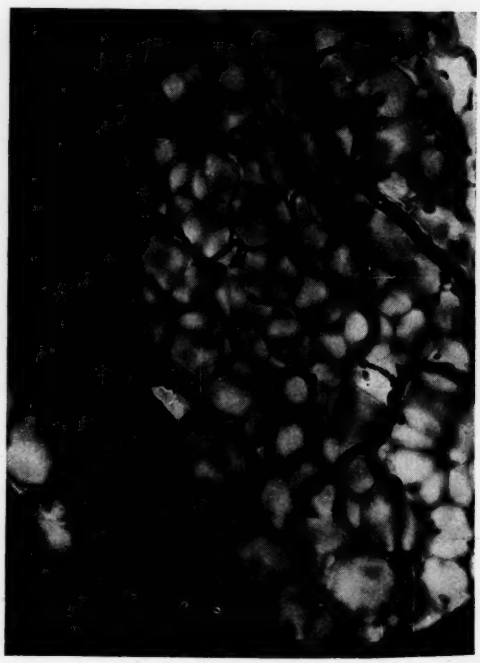
FIG. 409.—*Dogs* 7, 8.—Vividialysis: Histamine poisoning. Two dogs anæsthetized by morphia and nembutal connected to the dialyser and at Signal 1 circuit opened. *Dog* 7, lower curve; *Dog* 8, upper curve. Initial blood-pressure: *Dog* 7, 170; *Dog* 8, 130. Signals 2–7: Successive doses of 5 mgrm. histamine in 10 c.c. water injected into the femoral vein of *Dog* 7. An immediate fall in blood-pressure which was maintained at a level of 40–60 for about an hour. The blood-pressure of *Dog* 8 declined, and 15 minutes after the injection of histamine into *Dog* 7 it was at 60, and 45 minutes later *Dog* 8 died. Both showed at autopsy the evidences of histamine poisoning.

Using this apparatus we were able to observe in a series of experiments: (*a*) That trauma to *Dog* Y is without effect on the pressure of *Dog* X; and (*b*) That slow continuous intravenous infusion of histamine maintaining the pressure of *Dog* Y at shock level is accompanied by a fall of pressure in *Dog* X (*Figs.* 408, 409). These experiments appear to weigh strongly against the conception of any humoral



A. (× 80.)

B. (× 80.)

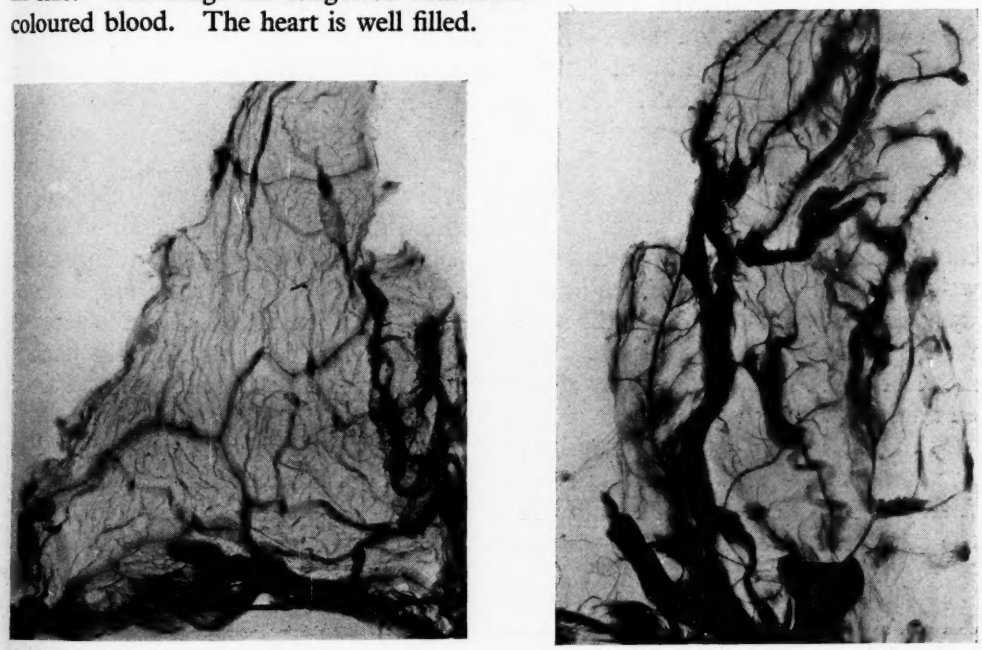


B. (× 190.)

FIG. 410.—Microphotographs of omentum in: A, Traumatic shock; B, Histamine poisoning.

agency, either produced locally in the area of trauma or more remotely, bearing a causal relationship to the development of traumatic shock. One reservation must be mentioned. The circulation toxin might be of so complex a molecular structure as to be incapable of dialysis across a collodion membrane. Only one active vasodilator principle identified in tissue extracts is known to be non-dialysable. The chemical nature of kallikrein, as it is called, is not yet known. It has been identified by characteristics of physiological activity different from those of histamine. Significantly for our purpose, it is rapidly inactivated by normal serum.

4. **Pathological Picture in Histamine Shock and Traumatic Shock.**—The post-mortem appearances in animals whose death has followed the administration of histamine differs significantly from those seen after death from traumatic shock. After histamine poisoning general examination of the abdominal viscera discloses striking features. There is a dusky diffuse congestion of the intestines. The cut surfaces of the liver and kidneys bleed readily. The omentum is engorged and presents large vessels macroscopically visible in the fat streaks. There is an intense œdema of the pancreas. The spleen is generally blue in colour and small in size. The lungs are congested with dark-coloured blood. The heart is well filled.



A. B.

FIG. 411.—Macroscopic specimens of omentum in: A, Traumatic shock; B, Histamine poisoning.

In striking contrast to this, the characteristic feature after death from traumatic shock is a general pallor of the viscera, especially of the intestines, and of the omentum. The liver and kidneys do not bleed readily when cut. Œdema of the pancreas is never observed. The spleen is contracted, but red in colour. The lungs are generally pale. The heart contains little blood. Frequently the left ventricle is in a state of tonic contraction.

Rich examined the capillaries in the omentum in cats. He demonstrated that when histamine is injected in amounts sufficient to produce shock a progressive

dilatation of the visible capillaries is observed, with opening up of a large number of occult capillaries. There is also a dilator effect on the immediately adjacent arterioles and venules. This constitutes a direct confirmation of the site of the action of the drug, as postulated by Dale. We have examined preparations of the omentum fixed *in situ* by flooding the peritoneal cavity with formalin-saline in animals subjected to trauma and in others after toxic doses of histamine. The dilatation of the peripheral vascular bed in histamine shock offers a striking contrast to the extreme degree of contraction of the capillaries and minute vessels in the case of traumatic shock. On microscopic examination under high power the dilated capillaries can only be found with difficulty after careful search in the 'shock' omenta; even the larger vessels are often very poorly filled with blood, as shown in the microphotographs (*Fig.* 410). The macroscopic contrast is well seen in cleared specimens of the omentum (*Fig.* 411).

SECTION II.—FLUID LOSS INTO THE AREA OF TRAUMA

In the experiments that provided the main basis for the toxic theory of shock, Cannon and Bayliss found that the fluid loss into the lacerated tissues was inadequate to account for the fall in blood-pressure produced by traumatizing one of the hind limbs of anæsthetized cats. As already mentioned, Blalock and Parsons and Phemister repeated these experiments and showed that the local fluid loss extended beyond the area of trauma into the groin and flank. They replaced the Cannon and Bayliss method of amputating by symmetrical incision through the upper thigh by amputation well above the area of swelling. The local fluid loss due to extravasation of blood and exudation of plasma, as expressed by the difference in weight of the injured and non-injured limbs after this hindquarter amputation, was sufficiently great to permit the conclusion that fluid loss itself sufficed to account for the decline in blood-pressure. Blalock found that he could produce the phenomena of shock in his animals by removing a corresponding amount of blood from an artery even when the animals suffered no trauma.

In *Table I* the details of a series of eight traumatized animals are given. *Fig.* 412 is a kymograph record of the course run in one of these animals. The average fluid loss into the traumatized limb in these animals, expressed as a percentage of the calculated blood volume, is 36 per cent. Macdonald and Holt give 51 per cent

Table I.—CONTROL EXPERIMENTS

CAT NO.	WEIGHT OF CAT	INCREASE IN WEIGHT OF TRAUMATIZED LIMB	FLUID LOSS EXPRESSED AS A PERCENTAGE OF CALCULATED BLOOD VOLUME	INITIAL BLOOD-PRESSURE	B.P. AFTER ONE HOUR	SURVIVAL TIME
	Grm.	Grm.		mm. Hg.	mm. Hg.	Hours
69	1500	55	48 per cent	160	60	$4\frac{1}{2}$
78	2500	58	30 per cent	195	150	3
88	2750	—	—	180	140	$3\frac{1}{2}$
83	3000	130	56 per cent	160	20	$1\frac{1}{6}$
50	3200	56	22 per cent	170	50	$2\frac{1}{2}$
76	4250	—	—	165	150	$6\frac{1}{2}$
20	3000	69	30 per cent	165	90	2
92	3000	53	22 per cent	135	110	2

for dogs and 43 per cent for cats. Including several other experiments not shown in the table, we obtained an average figure for the fluid loss in 12 cats of 32 per cent. When very severe trauma has been induced the fluid loss is sufficiently great to dismiss the need to invoke any other agency contributing to the production of shock. In some of our experiments, however, the fluid loss amounted only to about 20 per cent of the total blood-volume. In spite of this, the onset of shock in these animals was comparable in every way to that obtained by Blalock, both in degree of severity and in the rapidity with which death occurred. The degree of fluid loss into the traumatized tissues does not bear a direct relation to the survival time. These findings suggest that some other factor might be operative.

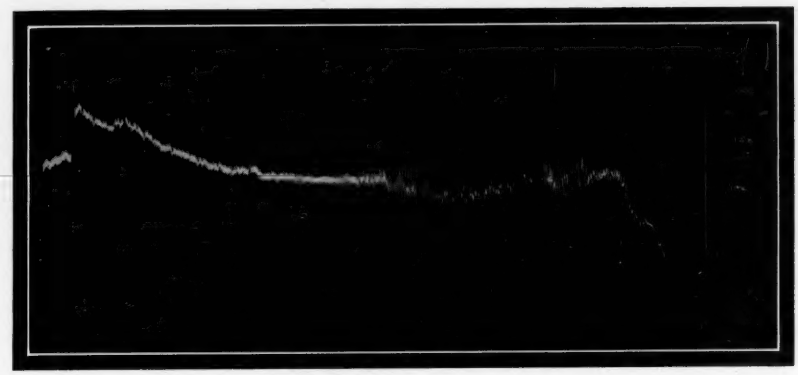


FIG. 412.—Trauma to thigh. *Cat* 92. 3000 grm. Chloralose. Tracheotomy. Initial blood-pressure 135. Signal: Trauma to thigh. Death 2 hours 20 minutes after trauma. 53 grm. increase in weight of traumatized limb. Time signal 30 seconds.

Many workers have shown that occlusion of the main vessels of a limb prevents the development of traumatic shock. We have found that when such occlusion is effected merely by ligature of the external iliac vessels a gradual decline in pressure manifests itself if the experiments are followed for an adequate period. Examination of the lacerated tissues and a comparison of the weights of the traumatized limb and of its fellow demonstrate that this procedure does not completely prevent hæmorrhage into the injured area. Collateral channels are obviously still operative. Complete occlusion of the blood-supply to a limb is only obtained by ligature of the abdominal aorta, the iliolumbar artery, the middle sacral, the external iliac, the profunda femoris, and the femoral artery and its branches in the groin. Complete obstruction of the venous return is only achieved by ligature of the inferior vena cava and the veins which correspond to the arteries enumerated above. To avoid repetition, we refer in the course of this account to such a preparation as an 'anæmic limb'. The total separation of such a limb from the general circulation can be demonstrated. Drugs injected into the muscles of such an anæmic limb are not absorbed into the general circulation. Trauma to the anaemic limb had no marked effect on the blood-pressure, although the animals were followed for many hours. An experiment in this group is illustrated by *Fig.* 413. The initial blood-pressure in this cat was 190 mm. of Hg, and seven hours after trauma was still 180 mm. of Hg. In the experiments in this group the animals were

followed for periods of eight to twenty hours, and in no case had the blood-pressure declined to a shock level.

The toxic factor having been excluded, these results have been used as evidence for attributing shock purely to fluid loss, since it is argued that shock fails to develop despite the fact that the nervous paths are intact. The integrity of normal pathways for nervous impulses from such a limb has been tacitly assumed. We find that after complete occlusion of the blood-supply the knee-jerks can no longer be elicited after half an hour, although the muscles still respond to direct stimulation. In short, the question to be settled is whether the 'anæmic' limb is not in fact also 'anæsthetic'. Although a much more detailed investigation is necessary before a final conclusion can be reached as to the functional efficiency of nerve endings and nerve trunks in the presence of an intense anæmia, it is unwise to assume that they are functioning normally. Although the sudden onset of shock on removal

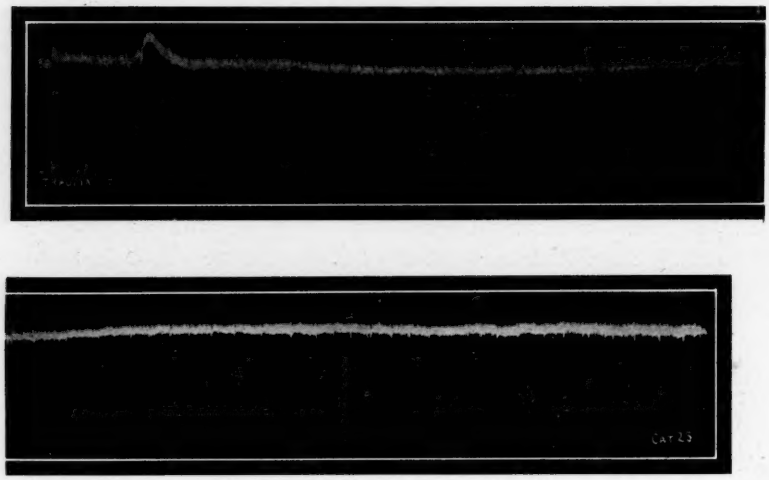


FIG. 413.—Trauma to thigh after ligation of vessels. *Cat* 25. 3000 grm. Chloralose. Tracheotomy. Initial blood-pressure 190. Signal: Trauma to thigh. Killed 5 hours later with a blood-pressure of 180. Difference in weight of limbs, 17 grm. Time signal 30 seconds.

of a tourniquet from a wounded limb might be attributed solely to the sudden loss of fluid as advocated by Blalock, it is also feasible that the sudden restoration of a blood-supply might be the signal for releasing a flood of nervous impulses.

Experimental support of this concept is provided by the following experiment. A cat (No. 43) was prepared in the usual way, and his right hind limb was rendered anæmic. A second cat (No. 42) was prepared. An anastomosis of the central end of his femoral artery to the peripheral end of the divided femoral artery of *Cat* 43 and a venous anastomosis were made simultaneously. In this way the anæmic limb of *Cat* 43 received a new blood-supply from the donor cat (42). The limb was then traumatized, as in other experiments. Trauma was followed by a progressive decline of the blood-pressure of *Cat* 42. His death followed some two hours later. Soon after this *Cat* 43 went into shock and died. At autopsy the organs of *Cat* 43 dripped blood on section. It was thus clear that fluid loss had not contributed to death. The efficiency of the vascular occlusion had previously been established by the injection of histamine into the anæmic

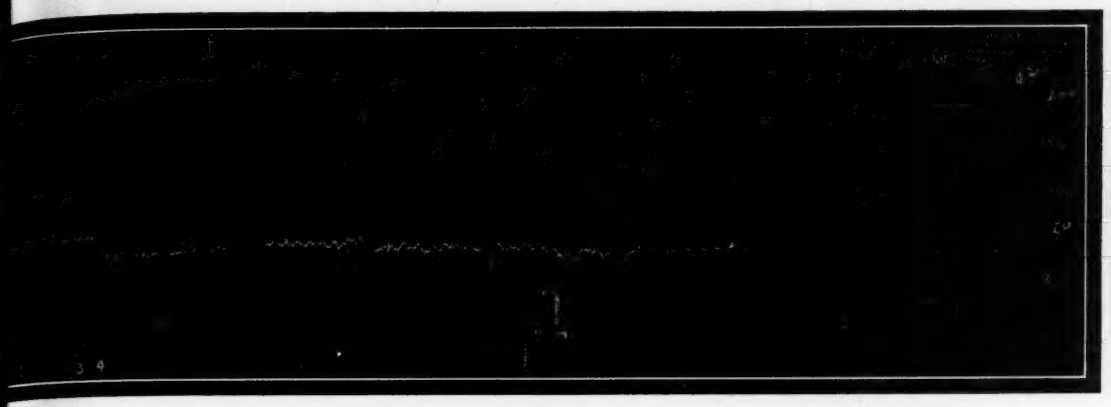


FIG. 414.—*Cats* 42, 43. Trauma to a limb excluded from the circulation but supplied with blood from a second animal. *Cat* 42 (upper tracing). 3500 grm. Chloralose. Tracheotomy. *Cat* 43 (lower tracing). 3250 grm. Chloralose. Tracheotomy. Signal 1, 2: 1 mgrm. histamine into thigh of *Cat* 43. Signal 3: Vascular anastomosis opened. Signal 4: Trauma to *Cat* 43. Signal 5: Massage of traumatized limb (*Cat* 43). Time signal 30 seconds.

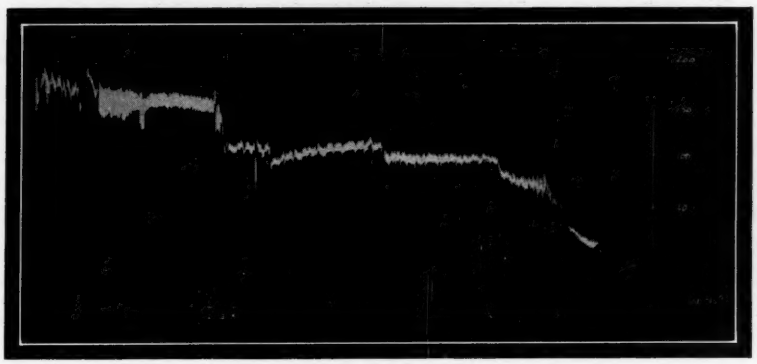


FIG. 415.—Ligature of vessels to limb—trauma—hæmorrhage. *Cat* 93. 3500 grm. Chloralose. Tracheotomy. Initial blood-pressure 185 mm. of Hg. Vessels to limb tied. Signal 1: Trauma. After 30 minutes blood-pressure still normal level. Signals 2–4: 10 c.c. of blood from subclavian artery. Signals 5–7: 15 c.c. of blood from subclavian artery. Death after loss of 60 c.c. of blood. Time signal 30 seconds.

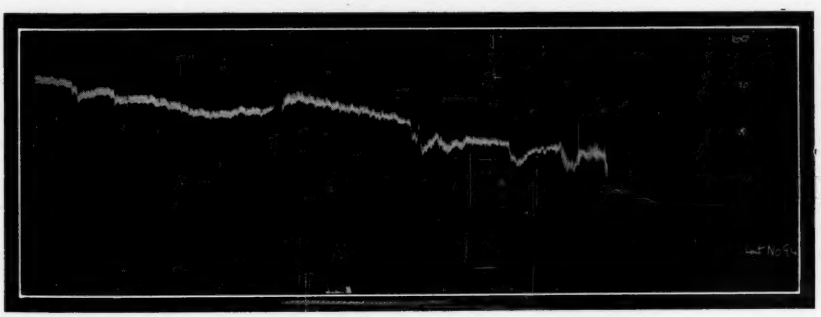


FIG. 416.—Effect of hæmorrhage on normal cat. *Cat* 94. 3500 grm. Chloralose. Tracheotomy. Initial blood-pressure 165 mm. of Hg. Signal 1, 2: 30 c.c. of blood from subclavian artery. Signal 3–12: 15 c.c. of blood from subclavian artery. Death after the loss of 105 c.c. of blood. Time signal 30 seconds.

limb. As there was no evidence of any incidental cause of death we are left with the presumption that the only remaining factor—nerve impulses from the traumatized area—led to the fatal event (*Fig.* 414).

A second type of experiment supports this view. Although anæmia of the traumatized limb prevents the onset of shock and a decrease in blood-pressure, the animal is affected by the trauma in a way which is not immediately demonstrated on the blood-pressure tracing. The limb is rendered anæmic, and at once—while the knee-jerks still remain active—trauma is applied and as usual there is no change in the level of the blood-pressure tracing; indeed, one hour after trauma its level was still, as originally, 180–190. At this point 15 c.c. of blood was removed from a cannula previously inserted into the subclavian artery. There was an immediate fall in blood-pressure and this fall persisted and was increased by successive bleedings, each of 10 c.c., until 60 c.c. had been removed, when the animal died. A control cat of equivalent weight not only withstood the loss of 105 c.c. before death ensued, but after each successive bleeding made a recovery—the difference in response of the two animals is shown in *Figs.* 415, 416.

SECTION III.—THE AREA OF TRAUMA AS A SOURCE OF NERVOUS IMPULSES

It is not our present intention to discuss the vexed question of primary and secondary shock. We are merely concerned with the course run by our traumatized animals. That course, like the clinical course of the patients whom we observed during this inquiry, did not permit of such a division. It has usually been assumed that the initial fall in blood-pressure after trauma is due to a nervous mechanism. Under some conditions this may be true, but often the initial fall is due to hæmorrhage into the traumatized area. We found that trauma to the anæmic limb was seldom followed by an initial drop in pressure even when this trauma was inflicted at a stage when a reflex arc, as demonstrated by the knee-jerks, was still present. On the other hand, in some of the animals subjected to a preliminary section of the cord or given spinal anæsthesia the initial drop was as marked as in the control animals, although the knee-jerks were absent (*Figs.* 417–419.)

The relation of the nervous system to the syndrome of traumatic shock has been investigated in a series of experiments which fall into the following groups: (1) Section of the nerves to the limb; (2) Section of the spinal cord; (3) Section and destruction of the spinal cord; (4) The induction of spinal anæsthesia. On examination of the four groups of experiments one fact emerges quite clearly: when an attempt had been made to exclude the nervous discharge from the area of trauma, the syndrome was less severe than in the control group. In the control group only one cat survived for as long as 6 hours, the average survival period was 3 hours 12 minutes, and each animal showed an appreciable drop in blood-pressure—in some cases 100 mm. of Hg—at the end of the first hour after trauma. In the group subjected to nerve section most of the animals ran so long a course that it was impracticable to follow them all to death. The average survival time of those which were followed to death was 5 hours 54 minutes. This includes the group subjected to cord section—an operation which in itself entails additional trauma—and the course run by those animals subjected to preliminary nerve section or spinal anæsthesia was much more favourable. We would emphasize in considering

the importance of the nervous factor that it is the course run by the animal over a period of hours rather than his *immediate* response to trauma which is significant. Perhaps some recent workers have failed to appreciate the nervous aspect of the syndrome because they have failed to appreciate this point.

FIG. 417.—Trauma to thigh: marked initial fall in pressure. *Cat* 50. 3250 grm. Chloralose. Tracheotomy. Initial blood-pressure 170 mm. of Hg. Signal: Trauma. Blood-pressure falls to 50. Death after 2 hours 20 minutes. Increase in weight of traumatized limb 56 grm. Time signal 30 seconds.

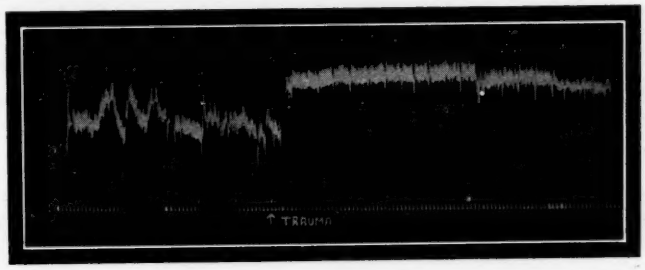


FIG. 418.—Ligature of vessels—trauma—rise in pressure. *Cat* 35. 3000 grm. Chloralose. Tracheotomy. Ligature of all vessels to thigh. Initial blood-pressure 190 mm. of Hg. Signal: Trauma. Pressure rises to 200. Time signal 30 seconds.

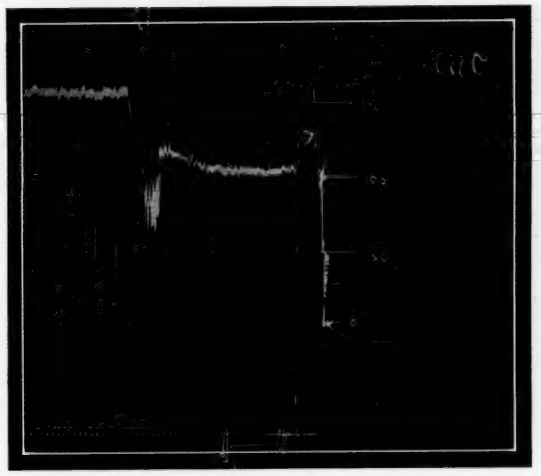


FIG. 419.—Trauma to thigh after section of spinal cord—marked initial fall in pressure. *Cat* 62. 4000 grm. Chloralose. Tracheotomy. Laminectomy and section of cord at D. 12. Blood-pressure 145 mm. of Hg. Signal: Trauma. Blood-pressure falls to 50. Time signal 30 seconds.

1. **Section of the Nerves to the Limb.**—Simonart's criticism of the original experiment by which Cannon claimed to demonstrate the onset of traumatic shock despite the preliminary section of the femoral and sciatic nerves has been summarized in our introduction. We repeated this experiment with two modifications: the obturator nerve was cut as well as the femoral and sciatic nerves, and as a preliminary to section the nerve trunks were infiltrated with 1 per cent novocain.

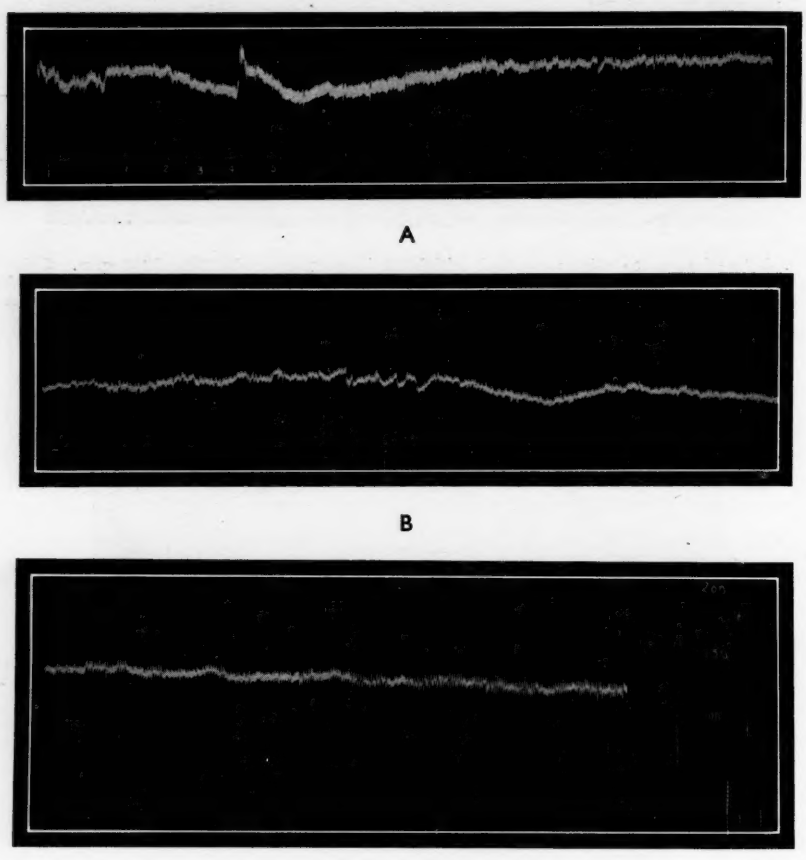


FIG. 420.—Section of femoral, sciatic, and obturator nerves: Trauma. *Cat* 99. 3000 grm. Chloralose. Tracheotomy. Section of femoral, sciatic, and obturator nerves. Blood-pressure 135 mm. of Hg. A. Signal 1: Clip on external iliac artery. Signal 2: Clip off external iliac artery. Signal 3: Clip on external iliac artery. Signal 4: Trauma. Signal 5: Clip off external iliac artery. B, The record 3 hours after trauma. C, 5½ hours after trauma. Blood-pressure 125. Animal killed. Increase in weight of traumatized limb 40 grm. Time signal 30 seconds.

When these conditions were fulfilled shock *failed* to develop. One cat was killed 6½ hours after his trauma with a blood-pressure of 130 (Initial B.P. 110) and another was killed 5 hours 20 minutes after trauma with a blood-pressure of 125 (Initial B.P. 135) (*Fig.* 420). In these two experiments the amount of local fluid loss was admittedly lower than usual (20 per cent), but we have the records of two control cats with an equivalent local loss of fluid, each of which died some two hours after the infliction of trauma. We have already explained our reasons for refusing to accept an exact parallelism between the local fluid loss and the degree of trauma.

2. **Section of the Spinal Cord.**—On the whole the animals subjected to section of the cord as a preliminary to trauma ran a less favourable course than did those subjected to nerve section or spinal anæsthesia. How far this may be due to the trauma involved, and how far to the fact that despite this procedure an effective interruption of all reflex arcs between the thigh and the splanchnic system is not attained, we are not yet in a position to judge. Nevertheless, one of the animals was still at a level of 100 mm. of Hg (Initial Blood-pressure 210) when it was killed 7½ hours after trauma, and in this case the fluid loss was 17 per cent of the calculated blood-volume.

3. **Section of the Spinal Cord with Destruction of the Lower Segment of the Cord.**—In only one of these animals was life prolonged for any appreciable time—it was killed 7½ hours after trauma with a blood-pressure of 85. The local fluid loss in these animals was less than in the control series.

4. **Induction of Spinal Anæsthesia.**—It became apparent that, in order to test the influence of the nervous system, some method less traumatic than section

Table II.—Spinal Anæsthesia Followed by Trauma

Cat No.	Weight of Cat	Increase in Weight of Traumatized Limb	Fluid Loss Expressed as a Percentage of Calculated Blood Volume	Initial Blood-pressure	Result
	Grm.	Grm.		mm. Hg	
39	2000	—	—	170	Killed after 4 hrs. B.P. 145
18	2250	35	20 per cent	175	Killed after 3 hrs. B.P. 120
17	3000	123	53 per cent	160	B.P. after 9 hrs., 125. Died after 10 hrs.
49	3000	69	25 per cent	120	Died after 8½ hrs. (Overdose of anæsthetic)
53	3800	—	—	165	Killed after 4 hrs. B.P. 120
54	4000	89	29 per cent	180	B.P. after 4 hrs., 100. Died after 9 hrs.
61	4000	55	16 per cent	170	B.P. after 3 hrs., 130. Died after 4 hrs. (Overdose of anæsthetic)
16	4500	—	—	140	Killed after 6½ hrs. B.P. 170
46	3250	—	—	170	Killed after 6 hrs. B.P. 140

FIG. 421.—Spinal anæsthesia followed by trauma. *Cat* 17. 3000 grm. Chloralose. Tracheotomy. A, 5 mgrm. novocain in 0·15 c.c. water injected intrathecally, L 4–5. Blood-pressure 150. Spinal anæsthesia maintained by injection every 30 minutes. B, Portion of record 4 hours after trauma. C, Signal Sp.: Final intrathecal injection. Death 9 hours after trauma. Increase in weight of traumatized limb 123 grm. Time signal 30 seconds.

or destruction of the spinal cord had to be devised. We also required a method which would effectively exclude the reflex paths between the thigh and the splanchnic region, as the operation of such a local reflex may well be one of the factors responsible for the appearances of the viscera and blood-vessels constantly found at autopsy and on laparotomy of the shocked animal. The only method that seemed to fulfil these conditions was the induction of spinal anæsthesia, and this method was therefore adopted. There is no doubt that this procedure has a most favourable influence in delaying and even preventing the onset of shock. At the same time, although spinal anæsthesia interrupts the nervous paths, both somatic and sympathetic, it has undoubtedly other effects on the vascular system—an increase in blood-volume has been observed by Schneider—and it must be admitted that its beneficial action may be due in part to these effects. For convenience, however, the results of our experiments with spinal anæsthesia in preventing the onset of traumatic shock and influencing its course will be described in this section.

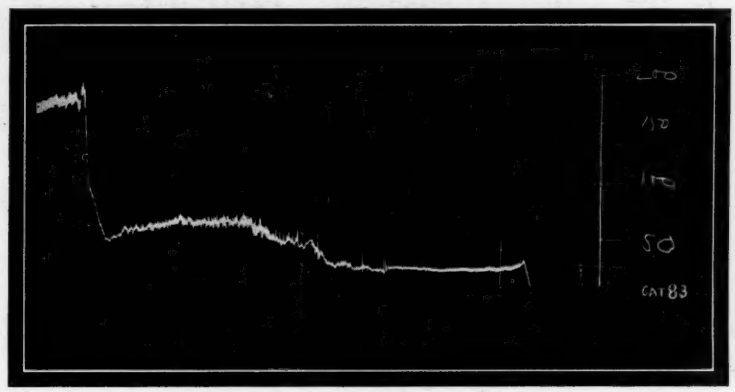


FIG. 422.—Trauma to thigh. *Cat* 83. 3000 grm. Chloralose. Tracheotomy. Initial blood-pressure 160. Signal: Trauma. Dead 1 hour 10 minutes later. Increase in weight of traumatized limb 130 grm. Time signal 30 seconds.

In 9 cats spinal anæsthesia was first induced and trauma was not inflicted until the knee-jerk had been abolished. The details of the course run by these animals is shown in *Table II.* In almost every case the blood-pressure at the end of the first hour had declined to a comparatively small extent, whereas in the control group a decline to a shock level (60 mm. of Hg) is usual within this period. Only three of these animals died within four hours, and in at least two of these death was probably accelerated by an overdose of intrathecal novocain. The remainder either survived for a period of eight or nine hours and, on cessation of the anæsthesia, went into shock and died, or were killed some six hours after trauma with the blood-pressure at a high level. The blood-pressure of one was higher than at the beginning of the experiment. The course run by *Cat* 17 is of particular interest; he survived for 9 hours, despite an unusually high fluid loss into the traumatized area (53 per cent). One of the control cats with a similar fluid loss died in $1\frac{1}{4}$ hours (*Figs.* 421, 422). A composite graph comparing the average course run by control animals with that of 'anæmic limb' and spinal anæsthetic animals is shown in *Fig.* 423.

Apart from the general decline in blood-pressure there is another characteristic which we have frequently observed. This consists of small variations in pressure shown by small irregularities on the tracing. It is absent from the

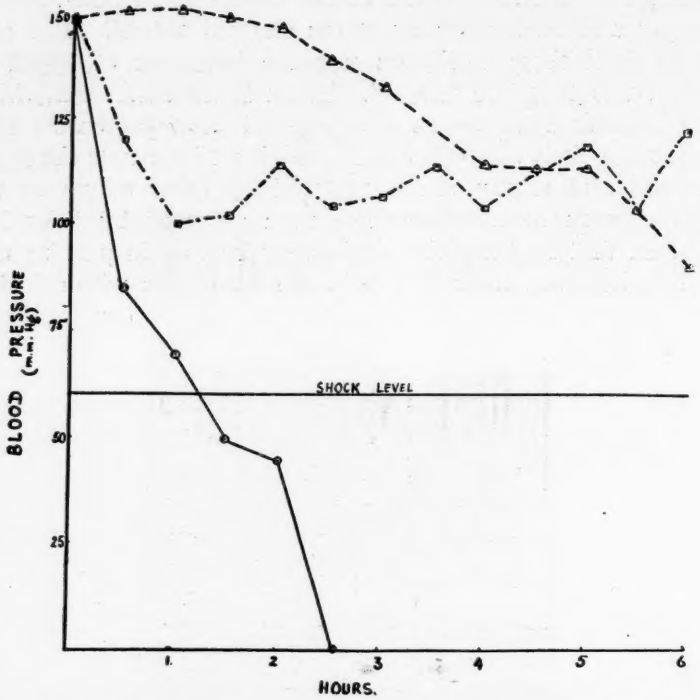


FIG. 423.—Composite graph of the course of animals subjected to trauma of the thigh. Control= ————. Trauma preceded by spinal anæsthesia = — · — · — · —. Trauma preceded by ligature of the vessels of the thigh = — — — — —.

tracing when the traumatized animal is under the influence of an effective spinal anæsthetic. The recovery from the spinal anæsthetic is marked not only by

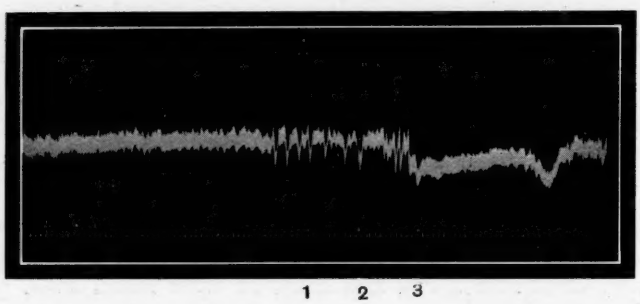
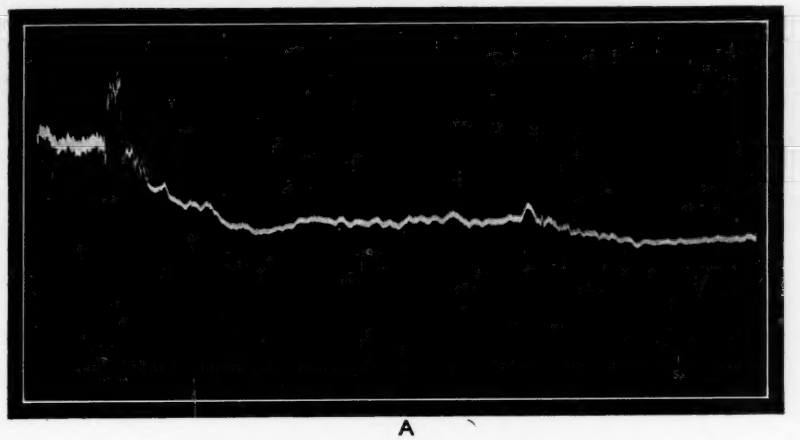


FIG. 424.—Trauma to thigh: Spinal anæsthesia. To show changes in blood-pressure. *Cat* 46. 3750 grm. Chloralose. Tracheotomy. At Signal 1: Knee-jerks present. Signal 2: Spinal anæsthesia. Signal 3: Knee-jerks gone. Time signal 30 seconds.

the return of the knee-jerks but by the re-appearance of these small pressure variations. We are not able to state the significance of these variations, but regard them as possible evidence of an abnormal reaction of a vasomotor centre subjected to a barrage of nociceptive impulses from the traumatized area—when



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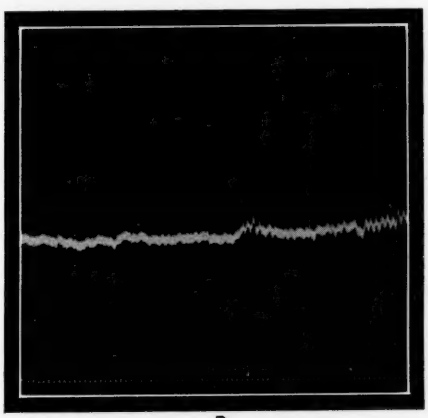

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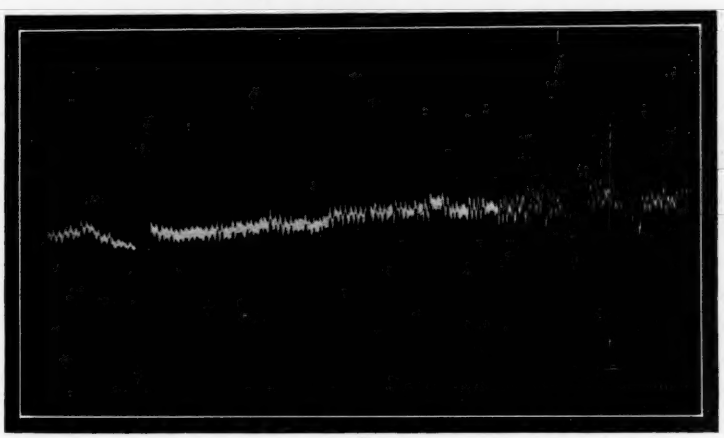

C

FIG. 425.—Trauma followed by spinal anæsthesia. *Cat* 57. 4000 grm. Chloralose. Tracheotomy. Initial blood-pressure 115 mm. Hg. A, Signal: Trauma. Blood-pressure falls to 50. Signal Sp.: Induction of spinal anæsthesia and this repeated at 30-minute intervals for 3 hours. B, Record 2½ hours after trauma. Signal: Induction of spinal anæsthesia. C, Signal: Knee-jerks present. Cat killed 5 hours after trauma with a blood-pressure of 100. Increase in weight of traumatized limb 116 grm. Time signal 30 seconds.

the barrage is lifted they disappear, only to return as it again becomes effective (*Fig.* 424).

Four animals were subjected to trauma and kept until the blood-pressure had assumed a shock level, when spinal anæsthesia was induced (*Table III*). In these cases there was a restoration of blood-pressure to well above a shock

Table III.—TRAUMA FOLLOWED BY SPINAL ANÆSTHESIA

CAT NO.	WEIGHT OF CAT	INCREASE IN WEIGHT OF TRAUMATIZED LIMB	FLUID LOSS EXPRESSED AS A PERCENTAGE OF CALCULATED BLOOD VOLUME	INITIAL BLOOD-PRESSURE	B.P. ON INDUCTION OF ANÆSTHESIA	RESULT
	Grm.	Grm.		mm. Hg	mm. Hg	
19	4750	—	—	200	90	Killed after 8½ hrs. B.P. 90
31	4000	131	43 per cent	135	50	Died after 5 hrs.
41	3750	90	31 per cent	170	85	Killed after 8⅓ hrs. B.P. 50
57	—	116	—	115	50	Killed after 5 hrs. B.P. 100

level, or a prolongation of the survival period, and one of the animals was killed 8 hours after trauma with a blood-pressure of 90 mm. of Hg. These results indicate the importance of the nervous factor, and it is of interest to note that the weight differences of the limbs in this group were high (*Fig.* 425.)

CONCLUSIONS

Again we would emphasize that the conclusions we are about to state apply solely to traumatic shock of the type defined at the beginning of this paper. We are not concerned with the etiology of the shock and collapse which may attend severe burns or trauma to the intestines. Indeed, we feel that a clear conception of the syndrome has been rendered difficult by attempts to establish a common etiological agent for such widely different states as the collapse which may follow a crushing injury of the thigh and the collapse which may be observed in an established case of intestinal obstruction. However, the experimental methods described above, especially the method of vividialysis, are peculiarly suitable for the investigation of any syndrome attributed to the circulation in the blood-stream of a toxic product.

Our first conclusion is that a toxæmia due to the elaboration of histamine, or any other depressor substance manufactured in the traumatized area, plays no part in the syndrome of traumatic shock.* We regard the two remaining

* The rejection of the toxic theory must suggest a reconsideration of gas and oxygen anæsthesia as contrasted with anæsthesia induced by ether. It is undoubtedly the fact that etherization leads to a more rapid death in histamine poisoning. This was one of the important considerations that led to the use of gas and oxygen for the shocked patient. The main essential in an anæsthetic, however, is that it should block nociceptive impulses. Unless it can be demonstrated that gas and oxygen forms an equally efficient barrier, its relation to histamine poisoning should no longer be taken into account.

factors, local fluid loss and the discharge of nociceptive nervous stimuli, as the effective etiological agents. The evidence does not allow us to dogmatize as to the relative importance of these factors, although we are inclined to believe that the nervous factor dominates the picture. It is extremely difficult to devise experiments which isolate the action of these two factors. The reaction of the anæmic limb to trauma has formed the basis for the view that local fluid loss is the predominating factor. As we have pointed out, the anæmic limb is also an anæsthetic limb, or at the very least a limb in which nervous reflexes are no longer normal. Again we would refer to the experiment in which shock was produced in an animal when the limb was excluded from its circulation but a second animal served to maintain its vascular supply and so its reflexes. In this case operation of the nervous factor alone produced shock as rapidly and as completely as did the operation of both factors together in the control animals. We have found it impossible to devise a converse experiment entirely free from logical objections, but in Experiment 17 (*see Table II*) this object was in some measure achieved. Despite a maximum fluid loss (the largest ever observed in our series of 100 experiments), the onset of shock was delayed for nine hours by the induction of spinal anæsthesia. While we must admit that this measure has possibly an effect on the humoral as well as on the nervous side, the practical applicability of the evidence is not impaired by any ambiguity with regard to its interpretation.

Work is still proceeding on the treatment of traumatic shock, and here we shall only outline the direction in which we consider that the accepted modes of therapy should be modified as a result of the conclusions reached in this paper. Our clinical experience, our experimental observations, and our study of the literature have convinced us that attempts to compensate for the fluid loss by means of intravenous therapy are largely ineffective. Up to the present, apart from the perfunctory administration of morphia, too little attention has been paid to the nervous side. The body itself possesses ample reserves of fluid, and the shocked case who recovers does so in large measure because he has been able to replenish a diminished volume by drawing on these natural resources. We have suggestive evidence to show that it is the continuance of abnormal nervous impulses which prevents this natural reaction on the part of the organism, and that if these impulses be controlled this favourable reaction takes place. The one therapeutic measure which succeeded in raising and maintaining the blood-pressure of a traumatized cat whose pressure had sunk to 20 mm. of Hg was the induction of spinal anæsthesia. In some cases this measure has been combined with injection of saline into the peritoneum, with apparently beneficial results. It is of course possible that some better method of controlling nociceptive impulses may be devised—the injection of a local anæsthetic into the traumatized area suggests itself as one possibility—but we are convinced that control in some form is essential to the successful treatment of the syndrome. Even if we are wrong in the emphasis we lay upon the discharge of nociceptive impulses, the beneficial effect of spinal anæsthesia remains a fact which seems worthy of note and further investigation.

This work was carried out at the Buckston Browne Research Farm under the direction of the Master, Sir Arthur Keith, to whom we are indebted for constant advice and encouragement. The work followed on some earlier experiments made by one of us under the direction of Professor R. J. S. McDowall, whose advice has

been invaluable. In all the experiments described in this paper, Mr. F. Watson gave us most willing and valuable technical assistance.

We wish to make grateful acknowledgement for criticism of the draft manuscript to Sir Henry Dale and Professor P. W. D. Wilkie.

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SHORT NOTES OF RARE OR OBSCURE CASES

A CASE OF A TRUE HERMAPHRODITE

By HAROLD MORISON, Dryden, Ontario

'Hermaphrodite' is a broad term used to include a fairly large group of individuals in whom the development of the external genitals is such that it is difficult or impossible to determine to which sex the individual belongs. The term, generally speaking, includes two classes of pseudo-hermaphrodite, the androgynous and the gynandrous. These two groups, the one having testicles with certain female characteristics in the external genitals, the other having ovaries with certain male characteristics, include 95 per cent of all cases of so-called hermaphrodites.

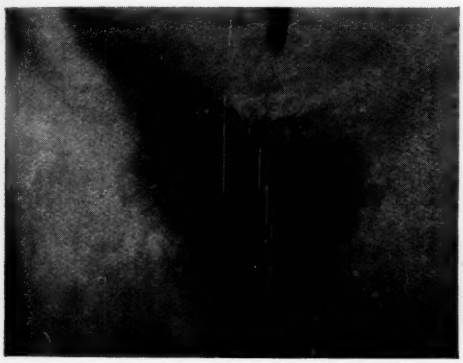

Fig. 426.—Showing distribution of pubic hair.

Fig. 427.—External genitalia. Note large clitoris protruding from vagina.

The true hermaphrodite is the individual who possesses, like the others, characteristics of the male and female on examination of the external genitals, but differs from the pseudo cases in that the individual has both ovarian and testicular tissues. The case here reported is, I consider, a case of a true hermaphrodite :—

A. N., Canadian born of Polish descent, age 26 years, labourer, came to me on Dec. 27, 1933, complaining of a severe pain in his right lower abdomen, and vomiting. After a careful examination I decided that this individual had acute appendicitis. He was subjected to operation and an acutely inflamed appendix was removed.

During the course of the examination certain points of interest were noted :—

1. The voice was soft, somewhat effeminate.
2. The features were characteristically male, a two-day growth of heavy black beard was noted.
3. The chest was quite flat, the nipples small.
4. The abdomen was flat, narrow waist tapering below to a broad pelvis,

definitely female in type. The distribution of the pubic hair was typical of the female (*Fig.* 426).

5. Examination of the external genitals (*Fig.* 427) elicited the following points of interest: A vagina, from the upper part of which protruded a large penis-like clitoris $1\frac{1}{4}$ in. in length. No scrotum or testicles were seen. The labia did not appear to contain any glandular tissue which might have suggested the presence of ovaries. There was no urethral opening in the enlarged clitoris. On raising the clitoris, however, one found a urethral opening at the junction of the base of the organ, and a groove which represented the vaginal orifice.

6. The legs were definitely female in type, heavy thighs, well-shaped calf and ankle.

It was decided to remove the appendix through a right rectus incision in order that a thorough examination of the pelvis could be made. On opening the abdomen I found on the left side of the pelvis a definite ovarian formation fixed in the pelvis. The intestines were packed off and retracted to procure a satisfactory view of the structure. It was white and nodular; no definite Graffian follicles could be seen. My assistants and I were quite certain that the structure was a fibrosed ovary. There was no broad ligament on the left side. In mid-pelvis there was no organ between the rectum and the bladder. I at first concluded that there was no uterine body present. In the right side of the pelvis, however, I found a mass of tissue the size of an orange, apparently of muscular formation, attached to what appeared to be a rudimentary broad ligament. This mass, which was very freely movable, was brought up through the incision and easily removed. I concluded that this mass was a uterus.

FIG. 428.—Photograph of the mass 4 × 3 × 6 cm. removed from right pelvis. The cut pedicle is at the bottom.

FIG. 429.—Section near base of mass showing dense fibrous capsule above and a few subjacent glands in looser connective tissue. (× 30.) (Azo-carmine stain.)

On careful questioning the patient stated that he had never experienced anything suggestive of menstruation, nor had he ever experienced sexual excitement or desire.

The specimen removed was sent to Dr. Daniel Nicholson, Assistant Professor of Pathology, University of Manitoba, for examination. The following is his report:—

The ovoid structure removed is shown in *Fig.* 428 and measures 4 × 3 × 6 cm. Its large size, its shape, and smooth peritoneal covering gave the impression that it was a uterus. Serial transverse incisions showed the tissues to be very firm and especially fibrous subjacent to the peritoneal surface. This excessive amount of connective tissues is confirmed by the microscopic examination of sections stained by azo-carmine, which stains connective tissues a deep blue and muscle and glandular tissues a pale purple (*Fig.* 429).

No evidence of uterine endometrium could be made out, but at widely separated intervals are islets of glands with masses of granular epithelioid cells adjoining them. These glands have the appearance of seminiferous tubules. Some of the cells lining the acini are definitely Sertoli cells, others which have no nucleoli

FIG. 430.—Two seminiferous tubules surrounded by a large aggregation of interstitial cells. (× 110.) (Eosin and hæmatoxylin stain.)

may be spermatogonia. The islets of granular epithelioid cells are the interstitial cells and they are present in greater numbers than in the average normal testis (*Fig.* 430). The increase of interstitial cells has been frequently observed in cryptorchids.

In sections taken from near the base of the mass there are some irregular-shaped ducts lined by dark-staining columnar cells. These are the rudimentary structures of the rete testis. Both Professor R. G. Inkster and Professor J. L. Jackson of the Department of Anatomy identified these structures as being rete testis.

Summary.—Large undescended testis containing a few areas of seminiferous tubules, an excess of interstitial cells, and much fibrous tissue. Operative findings combined with pathological examination of tissues removed places this case in the category of a true hermaphrodite.

PSOAS SPASM CAUSED BY A FOREIGN BODY

By T. G. ILLTYD JAMES, London

This case is recorded on account of the unusual features it presented.

R. C., an ill-nourished and neglected infant of 2 years, was admitted to hospital with a foreign body in his throat. There was no respiratory or œsophageal obstruction, but a skiagram revealed the presence of a large object in the pharynx, together with an assortment of foreign bodies in the abdomen. A large brooch was removed without difficulty from the pharynx, while the other objects were allowed to be expelled naturally—the usual treatment being administered. The needle in *Fig.* 431 (which shows the whole collection) was the last to be passed—seven days after admission, its course being watched by frequent skiagrams. The child was then discharged, none the worse for the experience.

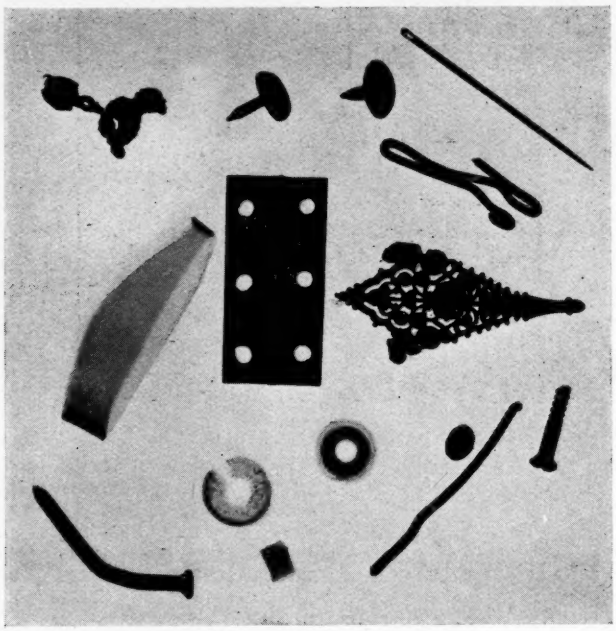

Fig. 431.—Foreign bodies passed naturally from the abdomen of a boy of 2 years.

Seven months later the boy was re-admitted for pain in upper part of right thigh and flexion deformity of right hip. The hip was acutely flexed, and attempts to extend it were painful. Further flexion and rotatory movements were free from pain. No other abnormality was discovered, and constitutional signs were absent.

A skiagram revealed a normal hip and spine, but showed the needle depicted in *Fig.* 432. Screening with a barium meal indicated that the needle was partly in the muscles of the posterior abdominal wall and partly in the duodenum. Laparotomy confirmed this diagnosis. The point of the needle could be felt in the transverse portion of the duodenum, with the greater part embedded deep in the right psoas muscle. The needle point was made to protrude through the

anterior surface of the duodenum. The most interesting feature of the whole case now presented itself, for the points of two needles protruded, in close apposition to one another. The needles were extracted, and the tiny hole was closed by a purse-string suture.

All pain and deformity at the hip disappeared after the operation, and convalescence was uneventful.

FIG. 432.—Skiagram showing position of needle.

COMMENTS

1. Perforation of the posterior surface of the duodenum by sharp foreign bodies which have been ingested is unusual. Psoas spasm from this cause must be very infrequent.

2. The complete superimposition of two needles of equal size, point to point and eye to eye, appearing in the skiagram as one, is a unique feature of this case.

ACUTE INTUSSUSCEPTION IN AN ADULT

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SURGICAL SPECIALIST, CYPRUS
AND M. GOSDEN
GOVERNMENT BACTERIOLOGIST, CYPRUS

ACUTE intussusception in the adult is a comparatively rare occurrence, and it is thought that there are unusual features in the following case which make it worth recording.

HISTORY.—The patient was a Greek woman aged 45. In March, 1932, she came to the Government Hospital complaining of a raised pigmented tumour just external to and below the right outer canthus. She stated that there had been since birth a small black mole in this situation, and that three months previously she had accidentally scratched it, since when it had enlarged rapidly.

On examination she presented a coal-black conical-shaped tumour approximately 2 × 2·5 cm. just below the right outer canthus and commencing to involve the lower lid (*Fig.* 433). A diagnosis of melanoma was made, and as she refused an operation the growth was treated by surface application of radium. A total dose of 1008 mgrm.-hours was given. She was seen again in July, 1932, when the growth had disappeared, leaving a smooth flat scar (*Fig.* 434). She was heard of from time to time as being quite well until April, 1934, when she

FIG. 433.—Melanoma of the face.

FIG. 434.—Appearance after treatment.

was admitted to hospital again with classical signs of acute intestinal obstruction. The duration of the symptoms before admission was thirty hours. She stated that six weeks previously she had had a similar attack which had passed off after twelve hours.

ON EXAMINATION.—The abdomen was soft and somewhat distended and visible peristalsis was marked. In the right iliac region a mobile indefinite tumour was palpable. P.R. and P.V. nil. Fæcal vomiting present.

OPERATION (April 10, 1934).—Mid-line subumbilical incision. The colon was found collapsed and empty, the jejunum was distended and intussuscepted about 8 ft. from the duodenal junction. It was found quite impossible to reduce this intussusception, and the affected gut was resected. Numerous pigmented deposits were seen in the mesentery and omentum. The patient did well for a few weeks and then succumbed to metastases.

EXAMINATION OF SPECIMEN.—The specimen consisted of a piece of jejunum 30 cm. long with a portion firmly intussuscepted into it. The walls of both the inner and outer layer were swollon and purple; no actual gangrene was present.

The apex of the intussusception consisted of a firm jet-black nodule 2 cm. in diameter. A similar smaller nodule was present in the wall 14 cm. from the apex (*Fig.* 435). Section of the nodule showed a typical secondary melanotic sarcoma in the wall (*Fig.* 436).

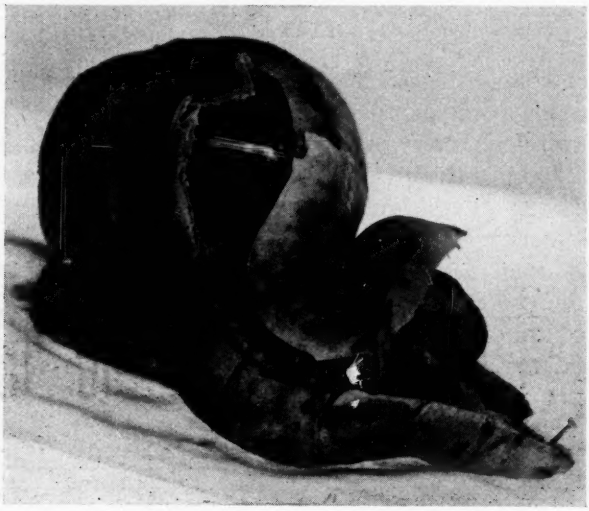

FIG. 435.—Portion of intussuscepted intestine.

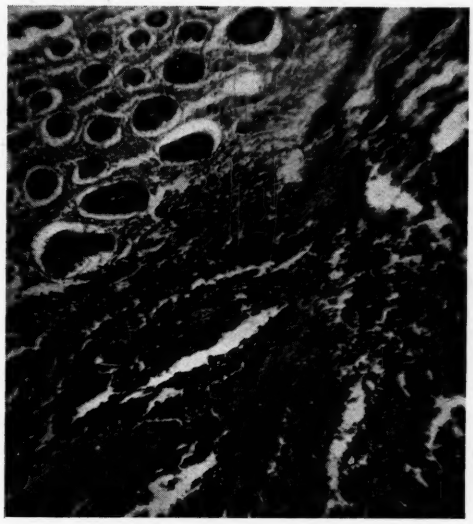

FIG. 436.—Section of growth in intestine.

SUMMARY

A case of melanotic sarcoma of the face is described, in which complete freedom from symptoms for two years followed treatment by radium. Acute intussusception occurred from secondary deposits in the small intestine.

MIXED TUMOUR ARISING IN THE PALATE

By T. FRANCIS JARMAN

LATE ASSISTANT MEDICAL SUPERINTENDENT, ROYAL SEA-BATHING HOSPITAL, MARGATE

THIS case is presented as being of rare occurrence and of very considerable interest both from clinical and pathological points of view.

A male patient, aged 17, was admitted to the Royal Sea Bathing Hospital suffering from abdominal tuberculosis. In the course of a routine physical examination a tumour of the palate was discovered. The patient was quite unaware of the presence of the tumour, had no idea of the date of its origin, and had, indeed, never been conscious of the presence of any abnormality in connection with the palate. The tumour was about the size of a walnut and situated in the centre of the soft palate; it was very firm in consistency, and though it appeared to be somewhat adherent on its deep surface to the hard palate and was not freely movable, it did not give the impression of actually arising from the hard palate.

OPERATION.—On May 30, 1933, an operation for removal of the tumour was performed. It proved to be extremely easy of removal and was enucleated without any difficulty. There was little bleeding, and the incision in the palatal mucous membrane was lightly sutured with fine catgut. Healing occurred rapidly by first intention.

PATHOLOGICAL FINDINGS.—The tumour was about the size of a walnut, of a slightly lobulated and irregular spheroidal shape, very firm in consistency, and surrounded by a fairly thick well-formed fibrous capsule.

On section the cut surface was smooth, dense, and of a white colour, throughout which were scattered a few small yellowish areas of a hyaline appearance.

Microscopic examination of a section of the tumour showed that it was surrounded by a well-formed fibrous capsule and that it consisted in part of cells with darkly staining angular nuclei, which cells were arranged in some places in irregular branching columns and in others showed a tendency towards duct and acini formation; and in part of areas showing degenerative changes and metaplasia resulting in the formation of myxomatous material and pseudo-cartilage (*Figs.* 437, 438).

The tumour thus appeared to be exactly comparable with the so-called mixed tumours, the origin of which is more commonly associated with the parotid and submaxillary salivary glands.

SUBSEQUENT PROGRESS.—Communication was made with the patient on May 10, 1934, in reply to which he volunteered information to the effect that the palatal wound remained soundly healed, that there was no evidence of any lumps whatsoever at the site of removal of the tumour or anywhere else in the mouth, and that no lumps or swellings were evident in the neck or elsewhere—sufficiently definite and reliable information on which to conclude that so far, after the lapse of one year from the time of removal of the tumour, there is no evidence of the presence of any recurrence.

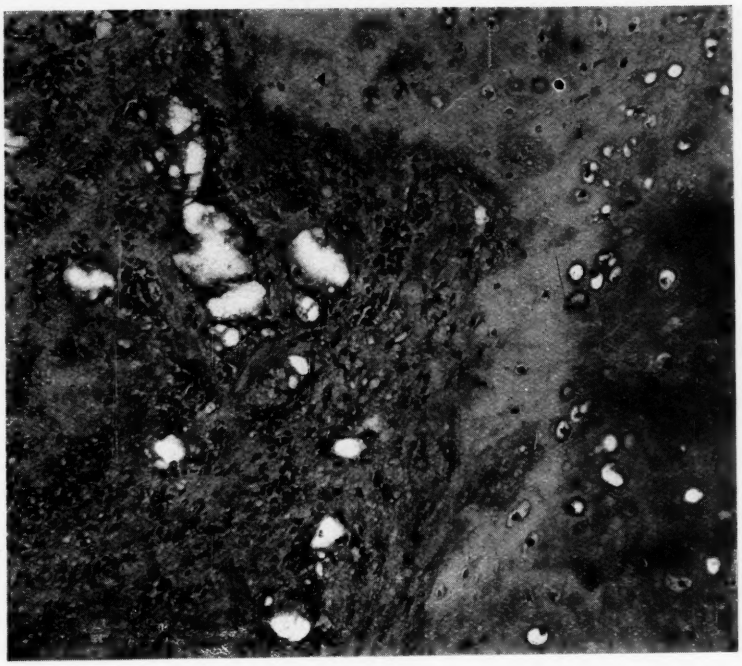

FIG. 437.—Photomicrograph showing irregular columns of cells with darkly staining angular nuclei, areas of myxomatous degeneration, and a large area of pseudo-cartilage. (× 90.)

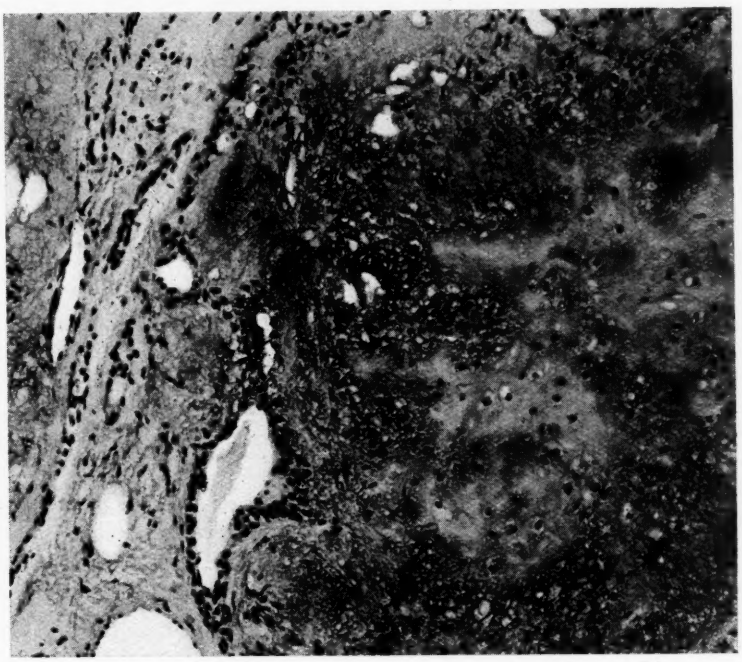

FIG. 438.—Photomicrograph showing tendency towards acini and duct formation, and some areas of pseudo-cartilage. (× 90.)

COMMENTS

Tumours of the so-called mixed type, the origin of which is usually associated with the salivary glands, are of extremely rare occurrence in the palate. D. H. Patey,[1] in an authoritative and exhaustive article, considers these 'mixed' tumours of the salivary glands from a pathological point of view; he found that of the 55 cases of mixed salivary tumours which he collected, 5 occurred in the palate. Of these 5, 4 have remained free from recurrence for some years and 1 developed a local recurrence two years after removal of the primary tumour.

R. Sonnenschein[2] has reported two cases and has reviewed the literature up to 1929. He states that mixed tumours of the soft palate are of comparative rarity, well within fifty cases. Of the two cases which he reports, one had an enormous growth in the soft palate which, when removed, looked like a uterine fibroid, and on section and microscopic examination showed "epithelial sheets resembling carcinomatous tissue, myxomatous tissue, alveoli filled with colloid, epithelial pearls, etc." Other cases are reported by Beck,[3] Heitz,[4] Malan,[5] and Carruthers.[6] Beck's case presented a firm growth in the right side of the palate, extending into the supertonsillar and post-nasal space. Biopsy revealed a "myxo-fibro-chondroma"; enucleation was performed, but recurrence took place three weeks later, which recurrence was successfully treated by electro-coagulation. Professor Malan describes one of his two cases as a "myxo-lympho-angio-endothelioma" and the other as almost identical with this except that it presented also a "pseudo-sarcomatous zone". The histological appearance of the case reported by Carruthers is identical with that now presented.

The origin and pathological nature of these tumours has been widely discussed, and it has been suggested that those occurring in the palate arise from embryonic salivary rests. M. Creysel[7] regards these palatal tumours as arising from already existing salivary gland tissue, and considers also that the polymorphism is more apparent than real, being the result of interaction between an epithelial and connective tissue. D. H. Patey,[1] to whose excellent article all those seeking detailed information and discussion with regard to the pathological nature of these mixed tumours might well be referred, concludes that "they are a composite group of epithelial tumours the varying pathological features of which depend on the degree of differentiation attained, rapidity of division of the cells, and the amount of myxomatous change undergone by the epithelium."

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PHLEGMONOUS GASTRITIS

By C. JENNINGS MARSHALL, London

History.—W. T., a man of 54 years, was admitted to hospital for pneumonia on Dec. 12, 1932. Empyema was identified by puncture of the left pleural cavity on Jan. 11, 1933; it was drained by rib resection under local anæsthesia on Jan. 13. The organism was a pneumococcus; the reaction was of a very adynamic type, the temperature for ten days preceding drainage not exceeding 99°.

The recovery from the pleural infection was uneventful until Feb. 15, the tube having been removed and only a short sinus into the chest remaining; on that date the patient began to vomit; no food was retained and vomiting persisted in the absence of its administration. On Feb. 17 the patient looked ill and exsiccated, though not profoundly so. The mind was clear, and the complexion and lips were clean; the tongue was heavily furred and dry. At intervals of an hour or so a very striking vomitus was produced; it was a copious bright red jelly, transparent, and not admixed with any recognizable formed element. There was no pus, no bile, no stercoraceous material. The jelly was amphoteric to litmus.

On Examination.—The temperature was subnormal (and remained so both before, and for some seven days after the time of this examination). Physical signs were conspicuous by their absence. The pulse was 104, the respiration 20. The abdomen was flat, without visible peristalsis; there was resistance by the upper part of the recti, but without any notable tenderness. An enema produced flatus and a small fæcal result.

Diagnosis.—The nature of the vomit was obviously the clue to the case; absence of bile or other intestinal content showed it to be gastric; the mucus and blood without trace of acid secretion would be accounted for by an acute inflammation of the mucosa abolishing its function. Recollection of published cases of phlegmonous gastritis, however, recalled a far more desperate picture than the one present—in particular contrasting with the complete absence of pain in association with the vomit. The comparatively afebrile character of the empyema could be set off against this, and it was thought best to explore.

Exploration.—The stomach was diffusely and intensely œdematous and rigid, the swelling extending from cardia to pylorus and also into the gastro-hepatic omentum. The retroperitoneal tissues were œdematous and the glands enlarged. The thickness of the gastric wall was estimated at about $\frac{1}{3}$ in. The tissues were glistening and semi-translucent. Close inspection in places revealed a milkiness suggestive of leucocytic infiltration, but nowhere was there a localized pus collection. The peritoneal coat was smooth and shiny; there was no perigastric lymph deposit and no rolling up of omentum. No trace of gastric ulcer could be seen. The liver and gall-bladder were normal. There being clearly nothing to be done, the abdomen was closed.

After-history.—Following this 'demonstration in force', the patient made a complete and rapid recovery. Tided over by rectal saline, oral feeding was resumed on the fourth day after operation. The mucoid vomit gradually ceased, at no stage being accompanied by pus. The ultimate recovery was free from dyspeptic symptoms, which had not been present before the illness either.

COMMENTS

The term 'phlegmon' derivatively refers to a 'burning' or inflammatory swelling, and therefore, suppuration not being an essential in the definition, this instance of acute cellulitis of the gastric walls which resolved without formation of pus is an important addition to the clinical picture of the disease. In the literature the difficulty of diagnosis has always been insisted on; here it was clear enough, the only difficulty being the incompleteness of the published description of clinical variations.

As regards the pathogenesis, consideration for the progress of the patient obviously precluded opening the stomach to make further investigations. Diffuse and local forms of acute pyogenic gastritis are well recognized, associated with gastric ulcer, trauma, or carcinoma; there may be local or diffuse abscess formation, sometimes with perforative peritonitis, liver abscess, or empyema. In the case under consideration the presumption arises that this was an instance of pneumococcal phlegmon of the stomach, probably hæmic in origin.

SARCOMA GROWING IN A CALCIFIED ADENOMA OF THE THYROID

By H. W. L. MOLESWORTH, Folkestone

The following case appears worthy of publication on account of its rarity.

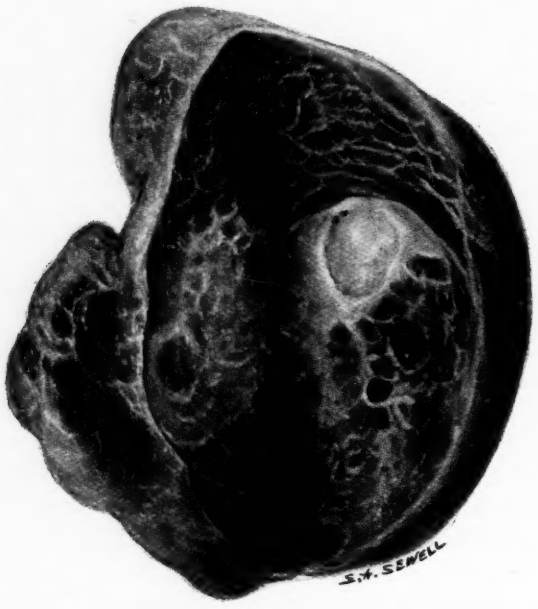

Fig. 439.—Calcified adenoma of the thyroid gland (*R.C.S.*, 7222.2).

A male patient, aged 59, complained of a swelling in the left side of his neck for one week. There was a hard nodule in the left lobe of the thyroid, about the

middle, which was not adherent to the surrounding structures, and there was no evidence of nerve involvement. At operation the whole of the left lobe of the thyroid was removed. The specimen was sent to the Royal College of Surgeons

FIG. 440.—Microscopical section of the tumour. (× 80.)

Museum, and on examination proved to be a calcified adenoma of the thyroid, from the capsule of which a spindle-celled sarcoma had developed (*Fig.* 439). *Fig.* 440 is a microscopical section of the tumour. The patient remains well at the time of writing, one year after the operation.

REVIEWS AND NOTICES OF BOOKS

Surgery of a General Practice. By ARTHUR E. HERTZLER, M.D., Chief Surgeon, Halstead Hospital, etc.; and VICTOR E. CHESKY, M.D., Chief Resident Surgeon, Halstead Hospital. Large 8vo. Pp. 602, with 427 illustrations. 1934. London: Henry Kimpton. 42s. net.

THE authors of this book, who are surgeons and not general practitioners, admit in their preface that they do not know what should be included in minor surgery, i.e., the surgery needful for a general practitioner, but they state that the scope of the book embraces such diseases and injuries as may be treated in the practitioner's office or the patient's home. The actual subject matter, however, far exceeds this definition according to the standards of this country.

Where true minor surgery is dealt with, i.e., such conditions as local injuries and infections, skin tumours, wound treatment, and the like, the methods advocated are on the whole satisfactory. It should be remarked, however, that no mention is made of the injection treatment of piles or of 'closed' drainage of empyema. Further, the suture of a fistula in ano after excision is advocated as a routine—this method, though valuable at times, is surely not advisable in the hands of a general practitioner.

Where more serious conditions are considered, such as carcinoma of the breast, tongue, and cervix, the advice given is crude and unsatisfying. The statement in reference to carcinoma of the cervix that "palliative measures—the cautery or acetone—may be used when a radiologist is not available or the patient does not have the price" is one which it is difficult to take seriously.

The Newcastle upon Tyne School of Medicine, 1834-1934. By G. GREY TURNER, assisted by W. D. ARNISON. Large 8vo. Pp. 224 + xii. Illustrated. 1934. Newcastle upon Tyne: Andrew Reid & Company Ltd. 10s. net.

THIS history may well serve as a model for other schools of medicine which from small beginnings as local proprietary teaching centres have developed into the medical faculty of one of the more recently founded universities. The Newcastle upon Tyne School of Medicine has been fortunate in its historians. Dr. Dennis Embleton published in 1890 *Collegium Medicum Novocastrense* and he joined the school five years after it was opened. Dr. Arnison became a student in 1882 and Professor Grey Turner in 1895. Each is able to speak from first-hand knowledge. The present writers summarize Dr. Embleton's history and carry it on until the present centenary year. Like St. Cuthbert, the school was itinerant for many years, moving from house to house until it seems at last to have found a permanent resting place with fully equipped buildings. It began from the very smallest beginnings, yet it soon secured recognition by the great licensing bodies at a time when such recognition was jealously guarded. The high standard of surgery which it quickly reached was due to the existence of the City Infirmary, where George Yeoman Heath, Rutherford Morison, and Grey Turner in succession found plenty of material upon which to teach, whilst the accidents and diseases incident to a rapidly increasing industrial population enabled them to attain a high standard of operative skill. Of all this the authors tell in a pleasant manner, and illustrate what they have to say with a wealth of pictures of the men and places they speak of. They also add a plan of the sites occupied at different times by the school of medicine. They provide also for the general reader two amusing and interesting chapters on life in the school in 1882–6, one written by Dr. Arnison, the other by Professor Grey Turner as he knew it several years later. All is now different. The type of student has changed, the eccentrics have vanished, but it is pleasant to have their memories recalled by those who knew them personally. As verbal corrections for the new edition which is sure to be wanted, it may be noted that Sir William Fergusson is uniformly spelt Ferguson and that Professor F. W. Andrewes was not Andrews.

The Science and Practice of Surgery. By W. H. C. ROMANIS, M.A., M.B., M.Ch. (Cantab.), F.R.C.S. (Eng.), F.R.S. (Edin.), Surgeon and Lecturer on Surgery, St. Thomas's Hospital, etc.; and PHILIP H. MITCHINER, M.D., M.S. (Lond.), F.R.C.S.(Eng.), Hon. Surgeon to H.M. the King, etc. Fifth edition. Royal 8vo. In two volumes. Vol. I, General Surgery. Pp. 789 + 75 pp. of index. Vol. II. Regional Surgery. Pp. 962 + 75 pp. of index. 758 illustrations. 1934. London: J. & A. Churchill. 14s. each volume.

THE fifth edition follows post-haste on the fourth. It is less than two years since it was our duty to review the latter, and what we then said might, with equal truth, be said of the present edition. Most of the chapters on the specialities or on special methods of investigation are up to date and modern in their outlook. The chapter on certain regions of general surgery are lamentably out of date: thus the sympathetic nervous system still receives scant mention, as does the present-day wire traction in the treatment of fractures, yet there is still room for the description of amputations which neither author can have ever seen performed. Has not the treatment of malignant disease by mass radiation made sufficient progress to be worthy of mention? It might with profit replace at least four out of the five methods of removing the tongue which have no present-day application.

We would again urge the necessity of re-writing certain chapters in view of recent progress, and the advantage to the publication which would result from the omission of all out-of-date methods of treatment.

Surgery of the Thorax. By T. HOLMES SELLORS, M.Ch., M.A., B.M. (Oxon), F.R.C.S., Assistant Surgeon to Queen Mary's Hospital for the East End, etc. Large 8vo. Pp. 519 + xxiii, with 140 illustrations. 1933. London: Constable & Co. Ltd. 22s. 6d. net.

THE necessity for a book on surgery of the thorax of reasonable size is unquestioned, and this fact affords sufficient justification for this review of the subject. Thoracic surgery has undergone such enormous developments during the last fifteen to twenty years that it is quite impossible in a volume of this size to do more than give a brief outline of the subject, but its value is increased by a good bibliography. The chapter on the physiology, which contains all the essentials of this subject, will repay reading by all those who perform even the occasional chest operation. Necessarily, there must be points which are debatable and with which the reviewer may not be in agreement, but there is such a complete lack of dogmatism that he is somewhat disarmed. In fact, for the surgeon who does occasional thoracic operations, it might be advisable if the author were more critical and dogmatic instead of offering a variety of procedures, many of which are of historical, and occasionally of minor historical, interest only. There is a very strong flavour of Continental surgery in the advocacy of extensive resections of the bony chest wall for certain types of thoracotomy. Many of these are surely unnecessary, and except where the chest wall is actually involved by neoplasms, restoration of the chest wall to as near normal as possible should be the ideal to be aimed at in so far as it compatible with efficient approach to the intrathoracic structures. Chapters are included on the heart, œsophagus, diaphragm, and aneurysm, apart from those devoted to pulmonary and mediastinal diseases.

The whole volume shows evidence of wide reading, is well written and printed, and the illustrations are admirably reproduced, and should form an excellent basis for those interested in the surgical side of chest disease.

Cirugiá gástrica. By Dr. MANUEL CORACHAN (Barcelona). Vol. I. Crown 4to. Pp. 775 + xiv, with 374 illustrations. 1934. Barcelona: Salvat Editores, S.A. No price given.

THE full value of this book cannot be appraised until the whole work is available, but much may be said about this present handsome volume. In the prologue Dr. Ribas Ribas, who also writes the introduction for his former pupil, the author, says that "at one stride, awakening (incipiente) Spanish Medical Literature attains the full height of the best foreign literature in quality if not in quantity". There is truth in what he says, but to those who know what Barcelona could produce in the way of books almost a hundred years ago (witness, for example, the history of the world in forty lavishly illustrated volumes published in 1845) this splendid piece of bookmaking will come as no surprise. The typography is excellent, the illustrations

are very good, and the binding is sound. Moreover, the contents deserve such form. This volume deals with preliminaries and clinical features; treatment is reserved for Volume II, so that the opportunity for appreciating the author's direct contribution to gastric surgery is so far restricted. Nevertheless, amidst a very complete exposition of contemporary opinion, Dr. Corachan's personality peeps out continually and with effect. After chapters dealing with anatomy, physiology, and embryology, the clinical examination of the 'gastro-duodenal' patient is taken and full accounts are provided not only of radiology (with beautiful pictures of the normal and abnormal mucosal patterns), but also of gastroscopy and gastro-photography.

In the chapter on the etiology and evolution of gastric ulcer, it is noteworthy that the author considers that ulcer-cancer is a not infrequent sequence. The later chapters deal with simple and specific gastritis, with tumours innocent and malignant, with gastroptosis, with gastric crises, pyloric spasm, volvulus, diaphragmatic hernia, diverticulosis, invagination, fistula, and injuries.

We look forward to the opportunity of reviewing the treatment volume, which will complete a great work.

Localization of Function in the Cerebral Cortex. By Various Authors. Vol. XIII of a Series of Research Publications. Editorial Board: S. T. ORTON, M.D., J. F. FULTON, M.D., T. K. DAVIS, M.D. Medium 8vo. Pp. 667 + xxi, with 171 illustrations. 1934. Baltimore: The Williams & Wilkins Company. (London: Baillière Tindall & Cox.) 36s. net.

THIS book constitutes Volume XIII of the annual reports of the meetings of the Association for Research in Nervous and Mental Diseases, and includes the papers presented at the thirteenth annual meeting of the Association held in New York on Dec. 28–29, 1932.

The contents may be divided into three sections. The first is devoted to the anatomy and comparative ontogeny of the cerebral cortex. The second deals with the physiological studies of the function of the cerebral cortex. The third section, which consists of the major part of the book, is concerned with clinical studies of a varied and wide nature.

It is impossible to review all the twenty-one chapters which go to make up this book, but some are of outstanding interest and importance.

Dr. Charles Frazier and Dr. Stuart Rowe contribute a most interesting and practical chapter on certain observations upon the localization in fifty-one verified tumours of the temporal lobe. These writers found that tumours in this so-called 'silent' area gave cortical localizing symptoms in 63 per cent of cases, whilst uncinate attacks were very uncommon. Another most interesting fact which emerges from this chapter is that over half the tumours of the left temporal lobe failed to produce aphasia.

Drs. Wilder Penfield and Joseph Evans have written a chapter on "Functional Defects Produced by Cerebral Lobectomies". These authors come to the conclusion that cerebral lobectomies, even though involving large amounts of brain substance, are followed by surprisingly little disturbance of function which can be detected by ordinary methods of examination.

The illustrations are very good, in fact they are themselves quite a feature of the book. The type is clear, and the format and general 'make-up' are excellent. The book will prove of value to the physiologist, neurologist, and neuro-surgeon alike, as well as to the anatomist who is interested in the cerebral cortex.

Actinotherapy Technique: An Outline of Indications and Methods for the Use of Modern Light Therapy. With a Foreword by Sir HENRY GAUVAIN. M.D., M.Chir. (Camb.), F.R.C.S. Crown 8vo. Pp. 184. Slough: The Sollux Publishing Co. 6s. net.

THIS small book serves a double purpose. In the first place it gives a brief account of the physical basis and physiological principle of 'light treatment' followed by an alphabetical list of the various conditions in which the method is useful, together with technical details for its application. Secondly, there are references to nearly 1000 books and periodicals which give first-hand descriptions of the scope and application of actinotherapy. It certainly forms an invaluable guide for the student and practitioner.

Die parasagittalen Meningiome. By Dr. H. OLIVECRONA (Stockholm). 10⅜ × 7⅜ in. Pp. 144, with 145 illustrations. 1934. Leipzig: Georg Thieme. Paper covers, M. 24; bound, M. 26.

DR. OLIVECRONA has done a real service to neurosurgery by the publication of this monograph on the parasagittal endotheliomata (meningiomata) of the cerebral hemisphere. The author has followed Cushing's lead in applying the term 'parasagittal' to those growths arising from the angle between the falx cerebri and the superior longitudinal sinus. Of the author's series of 82 cases of meningioma, 34 belong to the category under consideration. The clinical phenomena are discussed according to the exact site of origin of the tumour, whether from the anterior, middle, or posterior third of the longitudinal sinus, or from the lateral aspect of the falx cerebri below the sinus. A chapter deals with the morbid anatomy of these growths, but no detailed study is attempted of the histogenesis. There were 5 deaths out of the 33 cases submitted to operation, the causes being traceable to secondary infection associated with a cerebrospinal fistula (1 case), and pulmonary complications (2 cases.) A further 10 per cent of the patients died after an interval. More or less complete cure occurred in half the patients, while in a quarter there was a residual defect limiting their capacity for work. This monograph can be thoroughly recommended as a necessary addition to the library of every surgeon interested in neurology.

The Clinical Management of Horseshoe Kidney. By ROBERT GUTIERREZ, A.B., M.D., F.A.C.S., Chief of Clinic of the Department of Urology, James Buchanan Brady Foundation of the New York Hospital, etc. With a Foreword by Dr. EDMOND PAPIN (Paris). 10½ × 7½ in. Pp. 143 + xxiv, with 52 illustrations. 1934. New York: Paul B. Hoeber Inc. $3.00.

THIS monograph, the contents of which originally appeared in serial form in the *American Journal of Surgery*, contains a complete account of what is known on the subject of that congenital deformity called 'horseshoe kidney'.

As the result of his study of 25 cases the author has come to the conclusion that this condition is something more than just a malformation; he considers that its mere existence constitutes a disease, the 'horseshoe kidney disease'; this owns its characteristic signs and symptoms, and to obtain relief from these it is necessary to perform the operation of symphysiotomy, division of the isthmus uniting the two organs.

It is of interest to note that no fewer than 19 of the 25 cases were diagnosed before operation; of the remainder, 2 were discovered at operation and 4 at autopsy. This great improvement on the figures published by former authors must have been brought about by the recent advances in urography.

The author has devised a triangle to be used as an aid in the interpretation of skiagrams; its value is based on the fact that the lowest calices of the two kidneys are always much nearer to one another than in normally situated kidneys.

After reading the book with genuine interest the reviewer thinks that there are several statements which are open to criticism.

In spite of the author's assertion that the mere existence of a horseshoe kidney is sufficient to give rise to characteristic symptoms, it seems obvious, on reading the case histories, that every one of the 19 cases was suffering from some complication—infection, stone, hydronephrosis, or neoplasm. If the pain due to the fixity and 'incarceration' of the isthmus were of any severity, one would have expected the mean age of the patients to be something less than 30; the youngest was 18, and the majority were between 40 and 50.

It is difficult to follow the author when he states that the pressure of the isthmus, situated at the level of the bifurcation of the aorta, exerts a baleful influence on the cœliac plexus and the receptaculum chyli, and is it even certain that pressure on the sympathetic does cause pain?

Though Dr. Gutierrez is such an enthusiastic advocate of the operation of symphysiotomy as a cure for 'horseshoe kidney disease', it does not appear from this book that he has ever done one; two of the cases were treated, quite correctly, by heminephrectomy, and the others by dilatation of the ureters and lavage of the renal pelves.

The illustrations are beautifully reproduced, and the skiagrams are clear and helpful; there is a good and not too extensive bibliography and an index.

Le Genou. Anatomie chirurgicale et radiographique : Chirurgie opératoire. By Professor ANTOINE BASSET, Surgeon to the Beaujon Hospital, Paris. Royal 8vo. Pp. 189, with 120 illustrations. 1932. Paris : Masson et Cie. Fr. 45.

THIS small monograph on the anatomy and surgery of the knee-joint is comprehensive and well illustrated. The account of the anatomy both from the surface and by dissection is supplemented by radiographs of the normal joint in various positions and by a number of diagrams indicating the lines of all the important tendons and ligaments superimposed over those of the bones. These are drawn with great care and accuracy so as to make them of great value for reference. Another series of X-rays is given after barium injection of the synovial cavity and the arteries. About twenty different lines of incision for surgical approach are figured and described, together with the various methods of dividing the patella.

In the section dealing with fractures involving the joint, although the statement is made that it is desirable to reduce the number and size of foreign bodies used in osteosynthesis practised near a joint to the minimum, most of the illustrations given show that this principle has been grossly violated.

Most of the usual methods for suture of a fractured patella are described and illustrated, but there is no mention of the use of a pedicled strip of fascia lata as a suture material. In the operations for meniscotomy, the French method of making a long transverse incision dividing the lateral ligament is given a prominent place, without due reference to the danger that this method involves of weakening the stability of the joint. The repair of the cruciate ligaments and the different methods of arthrodesis and of arthroplasty are well described and illustrated.

The clearness of the illustrations, especially in the anatomical section, is one of the best features of the book.

Chirurgische Tuberkulose. By Dr. MAX FLESCH-THEBESIUS, Senior Medical Officer of the Surgical Section of the Private Hospital, Frankfurt a. M. With an Introductory Note by Prof. Dr. V. SCHMIEDEN. Medium 8vo. Pp. 194 + xiv, with 58 illustrations. 1933. Dresden and Leipzig : Theodor Steinkopff. Paper covers, R.M. 15 ; bound, R.M. 16.20.

THIS small book is an excellent summary of the subject of surgical tuberculosis. From first to last it is essentially practical, as befits a volume in the series of ' Practical Medicine ', of which it forms the fifteenth number.

In regard to the problem of diagnosis, the author takes very much the same view that is held in this country—that is to say, whilst acknowledging the value of various so-called specific tests, he does so with considerable reservation. Animal injection and biopsy each has a certain though restricted rôle in diagnosis.

Essentially the book is a description of the modern methods of treatment of surgical tuberculosis by the conservative methods of rest, fresh air, and light. Various methods of surgical fixation, e.g., Albee's bone-graft for the spine and different types of arthrodesis, are mentioned as having a limited application, but there is no description of their technique.

Manipulative Treatment for the Medical Practitioner. By T. MARLIN, M.D., Ch.B., D.P.H., R.C.P.S. (Eng.), D.M.R.E., Medical Officer in Charge of the Massage, Electro-therapeutic, and Light Departments, University College Hospital, etc. Demy 8vo. Pp. 133 + vii, with 86 illustrations. 1934. London : Edward Arnold & Co. 10s. 6d. net.

MANIPULATIVE treatment is usually interpreted by the medical writer as including movement of joints through their normal range, and stretching of ligaments and of muscles. The other manipulations of muscles and soft tissues are the work rather of the masseur. Therefore the more usual surgical manipulations are based upon a known pathology, adhesions are broken down, shortened muscles and ligaments are stretched. Even in the case of manipulations for a locked knee or temporo-mandibular joint we have a fairly clear idea of what is happening to the intra-articular cartilage. But the manipulations of the osteopath are in many cases based upon a much less definite and much more obscure pathology. Mr. Marlin has attempted the difficult task of describing and explaining manipulations of this class, with, it is to be feared, a result that is only partially successful. It is perhaps a pity that the greater

part of the book is devoted to the technique of manipulation, with only one chapter at the end on the choice of chronic cases for such treatment.

It is to be feared that the very wide difference between the medical and the osteopathic views of pathology makes it impossible to explain osteopathic methods in medical terms, but at least it is possible to study the clinical details in cases that are helped by manipulations as a guide to the prescription of treatment in other cases. Mr. Marlin's book fails to supply much that is still required, but nevertheless it does approach the subject of manipulative treatment from a new angle, it gives many useful details of methods, and it will therefore necessarily be read by all who are interested in surgical manipulations.

Infections of the Hand. A Guide to the Surgical Treatment of Acute and Chronic Suppurative Processes in the Fingers, Hand, and Forearm. By ALLEN B. KANAVEL, M.D., Sc.D., Professor of Surgery, Northwestern University Medical School, Chicago. Sixth edition. Pp. 552 + xvi, with 216 illustrations. 1934. London: Baillière, Tindall & Cox. 30s. net.

IT is twenty years since Kanavel began his studies on this subject, and the fact that his book has now reached its sixth edition proves that his teaching has been widely diffused. His two outstanding contributions to the correct understanding and treatment of infections of the hand have been: first, the distinction between lymphangitis and suppurative tenosynovitis, and second, the accurate description of the fascial spaces in the palm which are distinct from those of the tendon-sheaths. Both these teachings are now universally accepted. The present edition contains much new matter, such as that relating to infections from bites and injuries from the teeth, the pathology and treatment of metacarpo-phalangeal joint infections, of gangrenous infections, of injuries from indelible pencils, of cattle-hair and other peculiar infections. Chapters have been added upon the function of the hand, the use of splints, and the prophylactic treatment of injuries. One of the outstanding features of this, as of the former editions, is the beauty and clearness of the illustrations.

Röntgendiagnostik der Knochen- und Gelenkkrankheiten. By Prof. Dr. ROBERT KIENBÖCK (Vienna). Part 3. Gelenksosteomatose und Chondromatose. Large 8vo. Pp. 228, with 194 illustrations. 1934. Berlin and Vienna: Urban & Schwarzenberg. RM. 22.50.

THE third part of this series deals with osteophytes, cartilaginous and bony loose bodies in the joints, and malignant cartilaginous and bony tumours of joints. It consists largely of cases illustrated by radiographs and is more adequately illustrated than the previous numbers. It constitutes quite a good atlas of the subject, but unfortunately the diagnosis given is frequently open to question and subsequent operative findings are not always given.

Lord Lister: the Discoverer of Antiseptic Surgery. By C. J. S. THOMPSON, M.B.E., Hon. Curator of the Historical Collection of the Museum of the Royal College of Surgeons of England. Crown 8vo. Pp. 99. Illustrated. 1934. London: John Bale, Sons & Danielsson, Ltd. 5s. net.

THIS is a short account of the life and work of Lord Lister, written in a popular style suitable for the general public. It certainly fulfils its object of giving a brief account of the greatest of the movements of surgical evolution and of the personality of its hero in an interesting fashion readily understandable by the ordinary reader. Lister's modest character, his indomitable energy, and his steady progress to ultimate achievement and triumph are well told, so that the reader will probably go on to the perusal of the larger and more complete life by Godlee.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest for our readers.]

Surgical Applied Anatomy. By Sir FREDERICK TREVES, Bart., revised by C. C. CHOYCE, C.M.G., C.B.E., B.Sc., M.D., F.R.C.S., Professor of Surgery, University of London, etc. Ninth edition. F'cap. 8vo. Pp. 720, with 174 illustrations, including 66 in colour. 1934. London: Cassell & Co. Ltd. 14s. net.

Chirurgie du Pancréas. By P. BROCQ (Paris) and G. MIGINIAC (Toulouse). Large 8vo. Pp. 428, with 74 illustrations. 1934. Paris: Masson et Cie. Fr. 75.

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